UNIVERSITY OF ALBERTA

DIELS-ALDER REACTION OF 2-CARBALKOXY-8-METHYL-2-CYCLOOCTENONES AND SYNTHETIC STUDIES ON NEOLEMNANE AND NEOLEMNANYL ACETATE

BY

DAN-XIONG WANG ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta
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The undersigned certify that they have read, and recommend to the Faculty of Graduate studies and Research for acceptance, a thesis entitled **DIELS-ALDER REACTION OF 2-CARBALKOXY-8-METHYL-2-CYCLOOCTENONES AND SYNTHETIC STUDIES ON NEOLEMNANE AND NEOLEMNANYL ACETATE** submitted by **DAN-XIONG WANG** in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE.**

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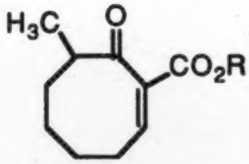
Date: October 28, 1996

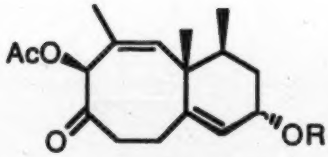
Abstract

Under Lewis acid catalysis, 2-carboalkoxy-8-methyl-2-cyclooctenone (**I**) was found to undergo Diels-Alder reaction with a variety of dienes to give directly the eight-six fused carbon ring skeleton possessing a functionalized substituent at the angular position. With unsymmetrically substituted dienes, the resulting angularly substituted adducts were found to be those predicted on the basis of the normal rules (*ortho* and *para*) governing the orientation of Diels-Alder addition. In some cases, the secondary orbital overlap of the diene with the ester carbonyl was preferred over the ketone carbonyl presumably due in part to steric effect. The degree of stereoselectivity was further shown to be dependent upon the substitution pattern of the diene, the Lewis acid, and even the sequence of addition of the reagents.

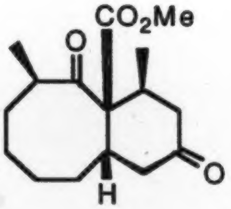
The results obtained in this investigation on the Diels-Alder chemistry of enone-ester **I** have led to the preliminary studies on a synthetic approach towards the total synthesis of neolemnane (**II**) and the structurally related natural product **III**. The key step in the projected synthesis is the construction of the fused bicyclo[6.4.0]dodecane carbon skeleton by a Diels-Alder reaction. The Diels-Alder adduct **IV** was obtained exclusively with the desired stereocenters. Adduct **IV** was treated with 1,2-ethanedithiol catalyzed by boron trifluoride etherate to give thioketal **V**. Hydride reduction of **V** furnished diols **VI** and **VII**. Several attempts have been made for the conversion of these diols to compound **VIII**.



I R = Me or Et



II R = H
III R = Ac



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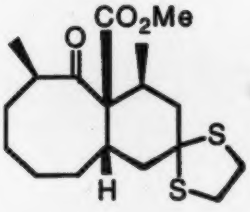

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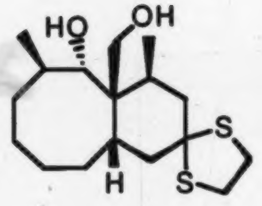

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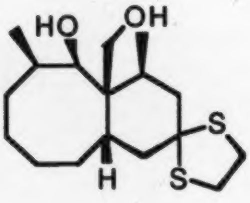

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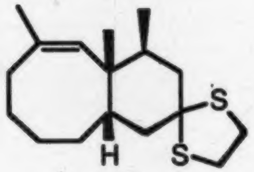

VIII

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To my wife Yue Wang

TABLE OF CONTENTS

Abstract
Acknowledgment
Table of Contents
List of Figures
List of Schemes
List of Tables
List of Abbreviations

Chapter One Diels-Alder reaction of 2-carbalkoxy-8-methyl-2-cyclooctenones

Introduction..1
Results and Discussion..17
Experimental..56
References..86

Chapter Two Synthetic studies on neolemnane and neolemnanyl acetate

Introduction..90
Results and Discussion..99
Experimental..120
References..140

LIST OF FIGURES

Figure 1. The NOE results of adduct **47**..........29

Figure 2. The possible conformations of cyclooctane..........34

Figure 3. Two possible conformations of enones **35** and **36**..........35

Figure 4. The conformational equilibrium of **B** and **C**..........36

Figure 5. The NOE results of compound **48**..........39

Figure 6. The NOE results of compounds **49** and **51**..........44

Figure 7. The NOE result of compound **53**..........45

Figure 8. The NOE results of compound **54**..........47

Figure 9. The NOE result of compound **57**..........48

Figure 10. The three dimensional X-ray crystallographical structure of compound **57**..........49

Figure 11. The NOE results of compound **56**..........50

Figure 12. The NOE results of compound **58**....................................51

Figure 13. The NOE results of compound **59**....................................52

Figure 14. The NOE results of compound **61**....................................54

Figure 15. The NOE results of compound **62**....................................55

Figure 16. The NOE results of diol **94**..104

LIST OF SCHEMES

Scheme 1. 2
Scheme 2. 4
Scheme 3. 6
Scheme 4. 7
Scheme 5. 18
Scheme 6. 21
Scheme 7. 92
Scheme 8. 92
Scheme 9. 93
Scheme 10. 94
Scheme 11 95
Scheme 12. 95
Scheme 13. 97
Scheme 14. 103
Scheme 15. 110
Scheme 16. 113
Scheme 17. 114

LIST OF TABLES

Table 1. Some examples of natural products containing eight-six fused ring system..14

Table 2. Diels-Alder reactions of 2-carbethoxy-2-cyclooctenone **33**...16

Table 3. Lewis acid catalyzed Diels-Alder reactions of enone **36** and 2,3-dimethyl-1,3-butadiene..28

Table 4. Lewis acid catalyzed Diels-Alder reactions of enones **35** and **36** and various dienes..30

Table 5. Diels-Alder reactions of 2-carbomethoxy-8-methyl-2-cyclooctenone (**35**) with dienes **45** and **46**...............................100

Table 6. Debenzylation results of compound **109**...........................116

List of Abbreviations

Ac	acetyl
APT	Attached Proton Test
Anal.	elemental analysis
Ar	aryl
Bn	benzyl
bp	boiling point
br	broad
°C	degree Celsius
calcd	calculated
^{13}C NMR	carbon-13 nuclear magnetic resonance
COSY	correlation spectroscopy
d	doublet
DIBAL	diisobutylaluminium hydride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
dt	doublet of triplets
eq	equivalent
Et	ethyl

g	gram(s)
h	hour(s)
HMPA	hexamethylphosphoramide
^{1}H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
M	molar
Ms	methanesulfonyl
m	multiplet
M^+	molecular ion
m/z	mass to charge ratio
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million

Py.	pyridine
R	generalized alkyl group or substituent
r.t.	room temperature
s	singlet
t	triplet
tert-	tertiary
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
TEA	triethylamine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl

Chapter One

Diels-Alder Reaction of 2-Carbalkoxy-8-methyl-2-cyclooctenones

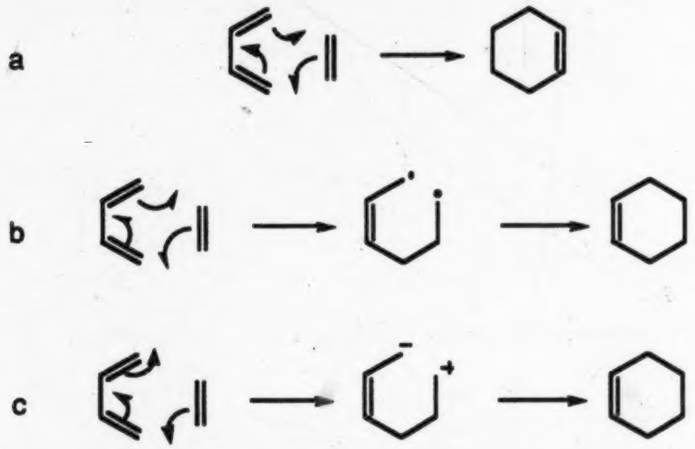
Introduction

The cycloaddition of olefin to conjugated dienes is a very useful method for the formation of substituted cyclohexenes. The reaction, which is easy, rapid, and of very broad scope, is known as the Diels-Alder reaction. It was first observed by Diels and Alder in 1928.[1] Since that time, the Diels-Alder reaction has been widely used in the total syntheses of many polycyclic natural products, for instance, in the classical synthesis of cantharidin,[2] cholesterol,[3] cortisone,[4] estrone,[5] and reserpine,[6] and thus gained prominence as a powerful synthetic tool. Recently, in our group, by the use of the Diels-Alder reaction, several interesting natural products, such as (+)-qinghaosu,[7] (-)-qinghaosu IV,[8] and two diterpenoids of the *cis*-clerodane family,[9] were successfully synthesized.

Although the Diels-Alder reaction has played a prominent role in organic synthesis, the detailed nature of its mechanism still remains in mystery. Generally speaking, three possible mechanisms (Scheme 1) have been considered for the uncatalyzed Diels-Alder reaction: mechanism ***a*** is concerted and occurs in one step with a cyclic six-centered transition state; mechanism ***b*** is a two-step process with a diradical intermediate which must be a singlet, i.e., the two unpaired electrons must have opposite spins; mechanism ***c*** , similar to mechanism ***b***, has a diion intermediate.

There have been many mechanistic investigations of the Diels-Alder reaction. Woodward and Hoffmann formulated this cycloaddition as a pericyclic and concerted electrocyclic process.[10] This formulation has received support from Frontier-Orbital calculations,[11] which successfully predicted the regioselectivity of the reaction. Even though the one-step cyclic mechanism ***a*** was supported by many experimental evidences, the diradical or diion mechanism still can not be totally ruled out. The main evidence in support of mechanism ***a*** is as follows: (1) The *cis*-addition is the most obvious and important character in Diels-Alder reactions. It is very stereospecific in both diene and dienophile. If the reaction undergoes in either mechanism ***b*** or ***c***, then it is impossible for the completely free diradical or diion intermediate to retain the configuration due to their rotation. (2) In general, the rate of Diels-Alder reactions is independent on the nature of the solvent. This would rule out a diion intermediate because the rate of reactions that develop charges in the transition state is deeply influenced by the nature of the solvent.

Scheme 1. The mechanism of Diels-Alder reaction



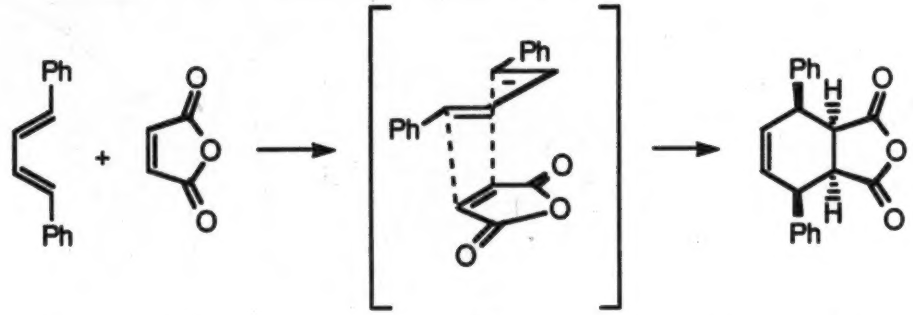
The electronic substituent effect has played a very important role in the rate of Diels-Alder reaction. From an electronic point of view, it is commonly regarded that the diene behaves as a nucleophile and the dienophile as an electrophile. Generally speaking, electron-donating substituents in the diene increase the rate of the reaction; electron-withdrawing groups decrease it. For dienophile, electron-withdrawing groups accelerate the reaction, and electron-donating groups retard it. However, this situation could be reverse. Thus, it is obvious that if a diene bearing an electron-withdrawing group is used, the most suitable dienophile should be the one in which electron-donating group(s) is presented. Apparently, in such a particular case,[12] diene is behaving as an electrophile while the dienophile is as a nucleophile. Such a reaction is called inverse electron demand Diels-Alder reaction.[13]

Over the years, with the in-depth investigation on the Diels-Alder chemistry, a series of empirical rules have been well developed. These rules have allowed the prediction of the structural outcome of the Diels-Alder reaction with great success. The development of these empirical rules has resulted in a dramatic increase in the application of the Diels-Alder reaction. Furthermore, the observations that catalytic amount of Lewis acid can greatly enhance the rate,[14] as well as improve the stereo-[15] and regio-selectivity[16] of the reaction have widened the scope and potential applications tremendously.

(a) The *cis*-principle

The *cis*-principle is an important feature that has been recognized from the reaction. It predicts that the diene and dienophile approach each other in approximately parallel planes and the addition is stereospecifically *syn*, with very few exceptions.[17] It also predicts that the relative configurations of the substituents in the transition states (for example, **3a**, Scheme 2) are preserved in the products. This can be illustrated by the reaction of *trans, trans*-1,4-diphenyl-1,3-butadiene (**1**) with maleic anhydride (**2**) to give the adduct **3** (Scheme 2) stereospecifically.[18] The *cis*-principle was classified by the Woodward-Hoffmann rules for a pericyclic reaction[10] as a concerted $2\Pi_s + 4\Pi_s$ cycloaddition reaction. In terms of orbital symmetry processing, this reaction is a symmetry allowed process. Furthermore, with respect to 1,4-disubstituted diene, this reaction is stereospecific and *syn* as indicated in Scheme 2. Thus the two phenyl groups are *cis* to each other in the product **3**.

Scheme 2

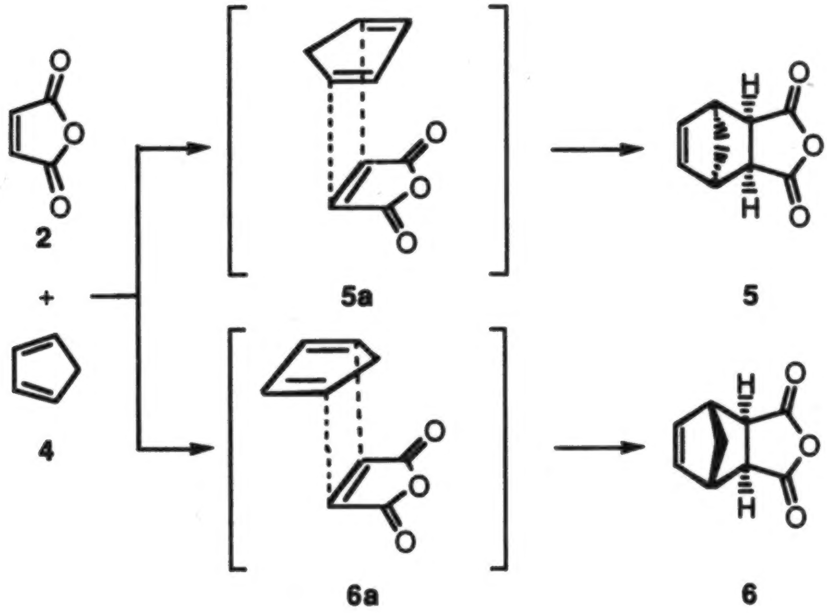


1 **2** **3a** **3**

(b) The *endo*-rule

The *endo*-rule was originally formulated for additions of cyclic dienes and dienophiles by Alder and Stein in 1937.[18, 19] It predicts that of the two possible "sandwich-like" transition states (for example, **5a** and **6a**), the more preferred would be that with the "maximum concentrations of double-bonds". Thus, reaction of 1,3-cyclopentadiene (**4**) with maleic anhydride (**2**) proceeds to give only the *endo*-adduct **5** and not the *exo*-adduct **6** (Scheme 3). This preference can be explained in terms of secondary orbital overlap between the π system of the diene and the directing substituent(s) of the dienophile. It has been well accepted that the transition state of this concerted process can be stabilized by secondary orbital overlap. In the *endo*-transition state **5a**, the directing substituents on the dienophile **2** are oriented toward the π orbitals of the diene **4**, leading to the formation of the secondary orbital overlap between these two π systems. The term "*exo*" therefore refers to the addition via the transition state (for example, **6a**) in which the directing groups on the dienophile are oriented away from the π system of diene and no secondary orbital overlap can occur. Except for the symmetrically substituted butadiene derivatives and dienophiles, the two transition states will lead to two different stereoisomeric products. The substitution pattern in the diene may determine the outcome of the products of *endo* and *exo* addition. In this concerted process, electronic and steric effects both contribute to and strongly influence the stereoselectivity of the reaction. Frequently, a mixture of both stereoisomers are obtained with one of the two products predominating. Generally speaking, the *endo* products are preferred especially when a dienophile bearing an unsaturated substituent, such as a carbonyl group, is involved. In this case, the electronic effect, i.e. the secondary orbital overlap, has the most important contribution in stabilizing the transition state, which can overcome the energy barrier as a result of steric interaction between the substituents of diene and dienophile. However, when a diene with bulkier substituents is involved, the interaction between the bulkier substituents on the diene and the dienophile will be strong enough to offset the stabilization effect presented by the secondary orbital overlap to force the substituent(s) of the dienophile to orient away from the π system of diene. In this situation, the *exo* product will be expected to dominate. Such a characteristic allows us potentially to be able to control the stereoselectivity of a Diels-Alder reaction, which means we can prepare a Diels-Alder adduct with the desired configuration by choosing the suitable substitution pattern in the diene. These explanations can equally be applied in acyclic cases.

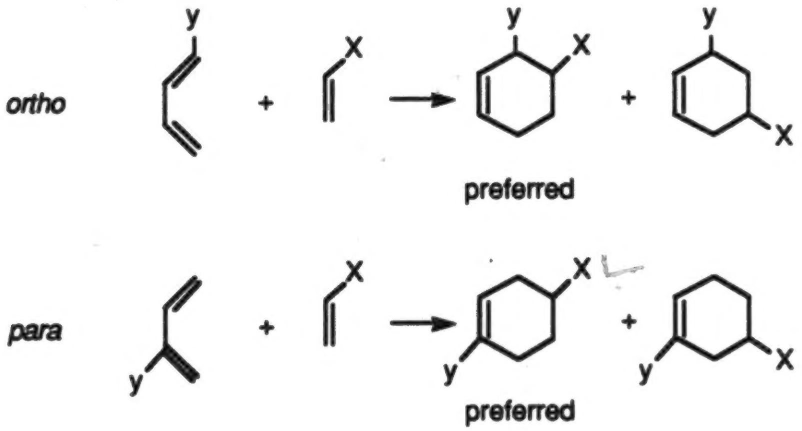
Scheme 3



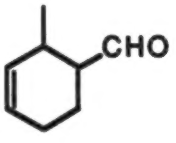
(c) The *ortho* and *para* rules

In the normal Diels-Alder reaction between unsymmetrical dienes and dienophiles, without counting stereoisomers, there are two possible products (Scheme 4). Although mixtures are often obtained, usually one regioisomer is predominant. This regioselectivity, in which the "*ortho*" or "*para*" product is favored over the "*meta* ", has been explained by Molecular-Orbital theory.[20] This series of orientation rules has greatly simplified the prediction of the structural outcome of the Diels-Alder reaction.

Scheme 4 The *ortho* and *para* rules



In the case of the reaction of a 1-substituted diene, the *ortho*-rule will operate to govern the reaction. The adduct obtained will be that in which the C-1 substituent from the diene is adjacent (*ortho*) to the substituent of the dienophile. Thus the principal adduct from the reaction of *trans*-piperylene with acrolein is adduct **7** rather than aldehyde **8**.



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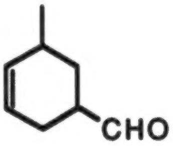
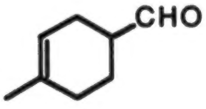


8

In the case of a 2-substituted diene, the structural outcome of the reaction is governed by the *para*-rule. The adduct obtained will be that in which the two substituents are in a *para*-relationship. For example, the reaction of isoprene with acrolein leads predominantly to the formation of adduct **9**.[21] The regioisomeric adduct **10** was obtained as a minor product.



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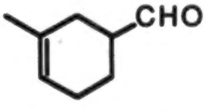

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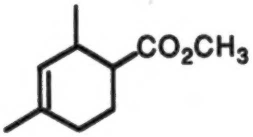
If a 1,3-disubstituted diene is used, the *ortho*- and *para*-rule operate in a complementary fashion and will give the adduct obeying both rules. For example, reaction of *trans*-2-methyl-1,3,-pentadiene with methyl acrylate gives **11** as the major adduct and **12** as the minor product.[21]



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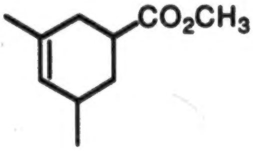
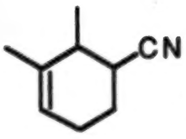


12

However, in the case of a 1,2-disubstituted diene, the *ortho*- and *para*-rule are in conflict and the *ortho*-rule will usually predict the course of the reaction. Thus, 1,2-dimethyl-1,3-butadiene reacts with acrylonitrile to yield adduct **13** as the major regioisomer and adduct **14** as the minor isomer.[21]



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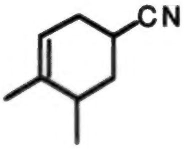
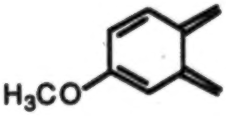


14

(d) The *meta*-rule

When the substituents of both diene and dienophile are electron-donating, the favored product should be the one in which the substituents are in a *meta* relationship. The experimental evidence of the "*meta*-rule" was achieved by Fleming.[22] Thus, the major product of the addition of ethyl vinyl ether to the diene **15** was adduct **16**.



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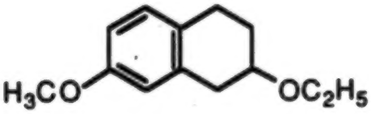
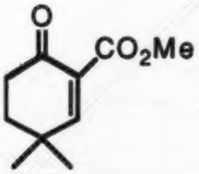


16

(e) Cisoid diene requirement

The *s-cis* conformation is required for the conjugated diene by the transition state of the pericyclic and concerted reaction. This *s-cis* conformation may be obtained from those dienes which have been either frozen into the cisoid conformation or able to achieve it during the reaction. If the diene is frozen into the transoid conformation, the reaction does not take place. Some investigations have shown that cyclic dienes, which have the frozen cisoid conformation, usually react faster than the corresponding open-chain compounds, which have to achieve the cisoid conformation by rotation during the reaction.[23]

In principle, the application of the Diels-Alder reaction in building fused polycyclic carbon skeletons requires only a straightforward addition of a cyclic dienophile to an appropriately substituted 1,3-butadiene. Furthermore, the high stereo- and regioselectivity of the cycloaddition potentially offers a direct and versatile approach to the construction of basic skeleton of a variety of natural products containing polycyclic system. It has been proven to be a powerful synthetic tool in the total syntheses of many polycyclic natural products. Unfortunately, the thermal cycloaddition of dienes to cyclic dienophiles, such as cyclohexenone, is a notoriously poor process.[24] Early investigations have demonstrated that thermal conditions often resulted in poor yields of the products. In order to improve the Diels-Alder reactivity of cycloalkenones, extensive investigations have been done and many methods of improvement were reported over the last thirty years. Of these, two major methods stand out for the enhancement of the dienophilicity of cycloalkenones.[25] One of these methods involves the application of Lewis acid catalysis. It has been observed that Lewis acid catalysis tremendously increases the rate of the Diels-Alder reaction[14] and has made available many adducts which were previously obtained with difficulty (sealed tube, high temperature, etc.). It has also been observed that such a catalysis has a profound effect on the regio- and stereoselectivity of the addition so that the *ortho*-[16c] and *para*-selectivity[16a-b] of the addition as well as the *endo*-selectivity[15] are markedly increased. The second method is the placement of an additional electron-withdrawing group on either the α- or the β-carbon of the dienophile. Kitahara and co-workers[26] reported on the aluminium chloride catalyzed addition of several dienes to 2-methyl-2-cyclohexenone. The aluminium chloride catalyzed Diels-Alder reactions of 1,3-butadienes with a series of cycloalkenones and 2-methylcycloalkenones have been reported by Wenkert's group.[27] Liu and co-workers have carried out an extensive study on the Lewis acid catalyzed Diels-Alder reaction of a variety of activated cycloalkenones including 5-, 6- and 7-membered cycloalkenones with a β-keto ester moiety (**17-30**).[28] In their research, the improvement of yields was observed in the Lewis acid catalyzed reactions. Furthermore, the dienophilicity of the cycloalkenones is considerably improved with the introduction of another electron-withdrawing group (for example, an ester group) at the α-position of the conjugated enone system. This was reflected in the shorter reaction time and the lower reaction temperature required as well as in the high yields obtained for the adducts. The outcome of these additions, in terms of stereo- and regiochemistry is, in general, quite predictable. In these studies common Lewis acids such as ferric chloride, tin(IV) chloride, zinc chloride, and boron trifluoride etherate were widely used and their effects on regio- and stereoselectivity of the Diels-Alder reaction were also examined. The studies also indicated the potential of using different Lewis acid catalysts to effect different regiochemical outcome in the reaction of isoprene with the dienophile **18**.[29] Thus, as outlined in Eq. 1, the addition of isoprene to **18** in ether at room temperature and under boron trifluoride etherate catalysis gave the adducts **31** and **32** in a ratio of 30 : 70. The formation of the abnormal *anti-para* adduct **32** as the major isomer has been rationalized by steric effect. On the other hand, by using stannic chloride as the catalyst, an 82 : 18 ratio of **31** and **32** was obtained. In this



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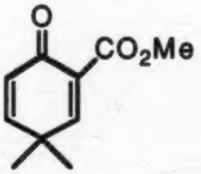

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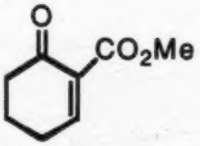

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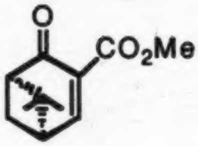

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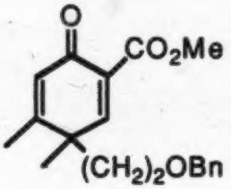

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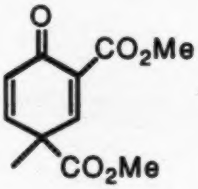

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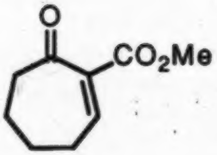

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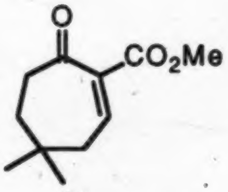

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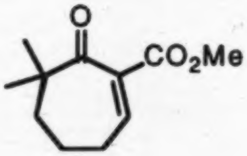

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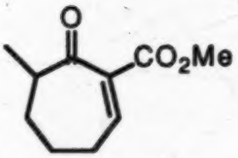

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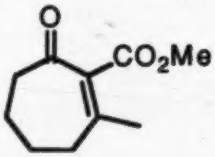

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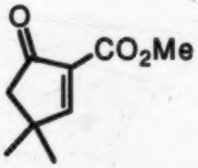

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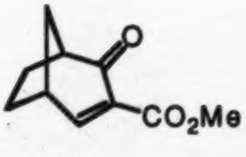

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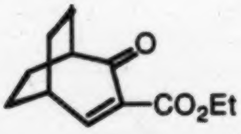
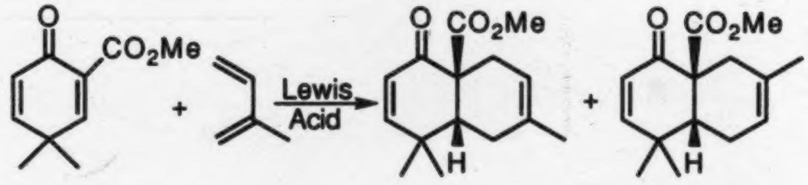


29

case, the normal *para*-adduct **31**, obtained as the major product, was formed by a dominating electronic effect extended by the bidentate stannic chloride on the keto ester moiety of **18**. This finding has facilitated the synthesis of α- and β-himachalene by the use of adduct **31**.[30]

Equation 1



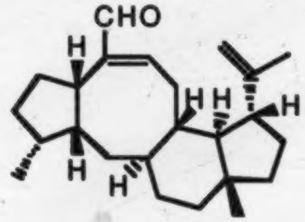
18 **31** **32**

$BF_3 \cdot Et_2O$	30	:	70
$SnCl_4$	82	:	18

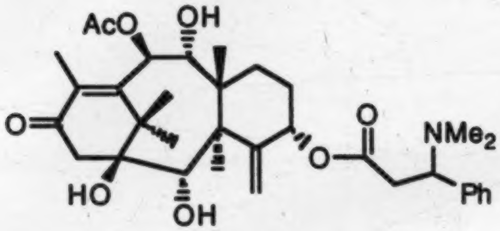
Although conjugated cyclohexenone and cycloheptenone having an additional electron-withdrawing group attached to the dienophilic double bond and their derivatives have been observed to display improved dienophilicity in the Diels-Alder reaction, so far there is no report on the use of 2-cyclooctenone and its substituted derivatives in the intermolecular Diels-Alder reaction . On the other hand, the development and application of effective modern separation and identification techniques have led to the discovery of more and more natural products possessing complex structure with a number of stereocenters. Thus, the interest in the development of a general methodology for the construction of the fused bicyclo[6.4.0]dodecane system has been stimulated considerably due to the discovery of many biologically active natural products containing eight-six fused ring skeleton (see Table 1 for examples).

In order to develop a facile and efficient synthetic approach for the construction of the fused eight-six ring system, Dr. J.B. Kim of our laboratory carried out an investigation on the potential use of 2-carbethoxy-2-cyclooctenone (**33**) as a dienophile in Diels-Alder reaction.

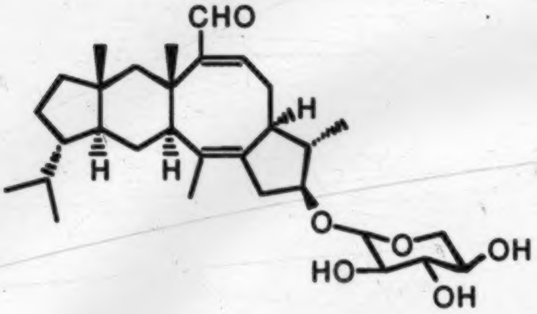
Table 1. Some examples of natural products containing eight-six fused ring system



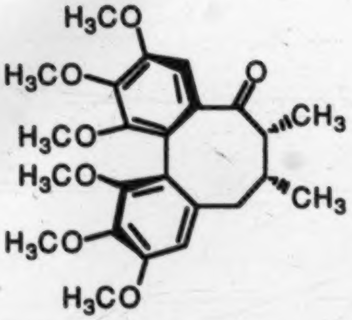
Variecolin[31]



Taxine B[32]



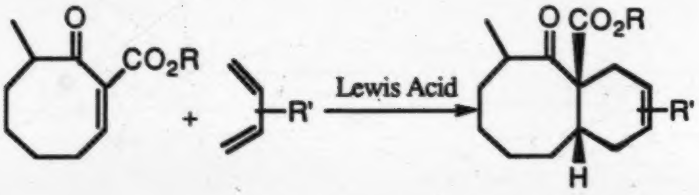
Aleurodiscal[33]



Schisanlignone A[34]

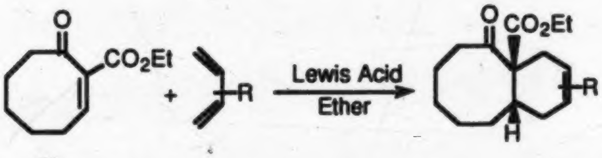
As indicated by the results compiled in Table 2, this compound was found to undergo Diels-Alder reaction readily with a number of representative dienes under Lewis acid catalysis to give, in general, adducts in synthetically useful yields. In continuation of our research in this area, the Diels-Alder characteristics of 2-carbalkoxy-8-methyl-2-cyclooctenone (**34**) (Eq.2) were examined. The results are discussed in this chapter of the thesis.

Equation 2



34 R = Me or Et

Table 2. Diels-Alder reactions of 2-carbethoxy-2-cyclooctenone (**33**)



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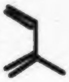
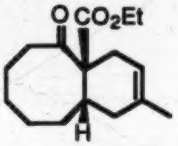
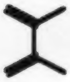
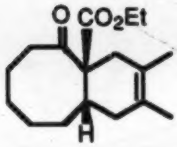
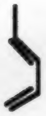
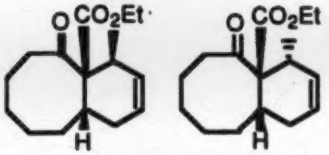
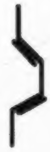
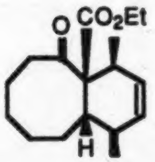
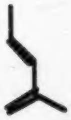
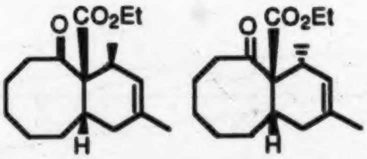
Entry	Diene (10 eq)	Time (h)	Temp. (°C)	Product	Lewis Acid[1]	Yield (%)
1		1/3 24 72 48 72	-20 -20 0 0 r.t.		$FeCl_3$ $SnCl_4$ $ZnCl_2$ $BF_3 \cdot OEt_2$ no L.A.	84 86 16 35 2
2		1/3	-20		$FeCl_3$	89
3		1/3 18	-20 -20	 85 : 15	$FeCl_3$ $SnCl_4$	80 89
4		24	-20		$SnCl_4$	23
5		1	-20	 77 : 23	$SnCl_4$	83

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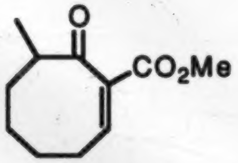
[1] Ferric chloride, tin(IV) chloride and boron trifluoride etherate were used in 1 eq. Zinc chloride was used in 2 eq.

Results and Discussion

I. The preparation of the dienophiles

Two routes have been developed for the preparation of the dienophiles, 2-carbomethoxy-8-methyl-2-cyclooctenone (**35**) and 2-carbethoxy-8-methyl-2-cyclooctenone (**36**). In each case, the α-methyl group was established by treating the starting cycloalkanone (cyclooctanone for **35** and cycloheptanone for **36**) with lithium diisopropylamide (LDA) followed by addition of methyl iodide.[35] For compound **35**, the carbomethoxy group was introduced by carbomethoxylation of 2-methylcyclooctanone with dimethyl carbonate.[36] For compound **36**, the carbethoxy group was established using Lewis acid catalyzed ring expansion of 2-methylcycloheptanone with ethyl diazoacetate.[37] The phenylselenenylation-oxidative elimination process[38] was chosen for the construction of the conjugated enone double bond.



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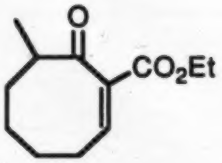

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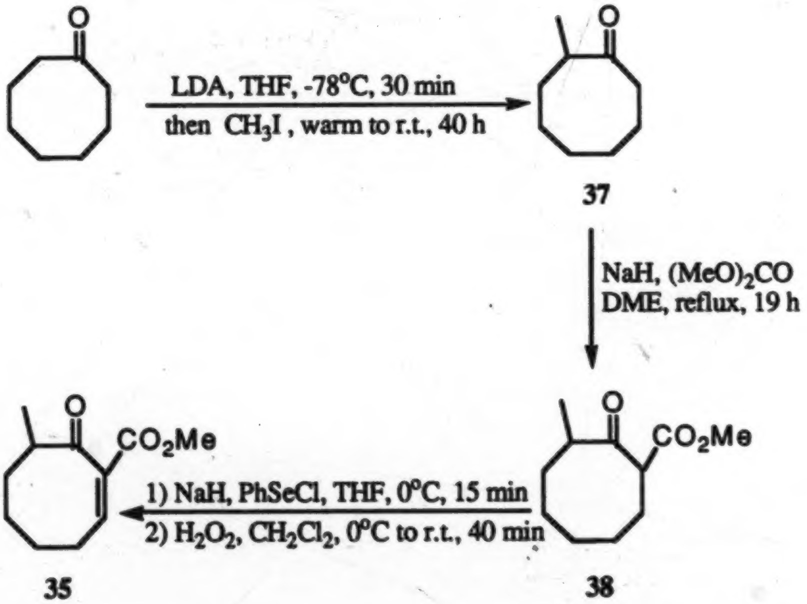
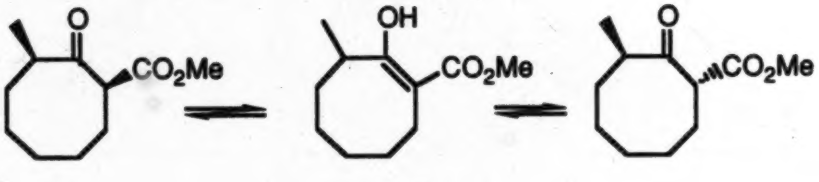
The preparation of dienophile **35** is schematically illustrated in Scheme 5. Treatment of cyclooctanone with LDA in tetrahydrofuran (THF) at -78°C, followed by addition of methyl iodide, gave compound **37** in 89% yield. In the proton nuclear magnetic resonance (^{1}H NMR) spectrum, it displayed a methyl doublet at δ 1.00 with a coupling constant of 7 Hz . The infrared spectrum confirmed the presence of a ketone carbonyl with a strong absorption at 1700 cm^{-1}. In the high resolution mass spectrum, a molecular ion peak at m/z 140.11977 was consistent with the molecular formula $C_9H_{16}O$.

Scheme 5. The preparation of enone **35**


O
LDA, THF, -78°C, 30 min
then CH_3I, warm to r.t., 40 h
O
37
NaH, $(MeO)_2CO$
DME, reflux, 19 h
O
CO_2Me
1) NaH, PhSeCl, THF, 0°C, 15 min
2) H_2O_2, CH_2Cl_2, 0°C to r.t., 40 min
O
CO_2Me
35
38

Compound **37** was treated with sodium hydride and dimethyl carbonate in refluxing 1,2-dimethoxyethane (DME). The desired product **38** thus formed exclusively in 85% yield was shown to exist as a mixture of two keto forms (2:1, total 68%) and an enol form (32%). The infrared spectrum confirmed the existence of ketone and ester carbonyl groups, showing absorption bands at 1707 (ketone), 1749 (ester) and 1640 cm^{-1} (C=O, ester of enol). The carbon-carbon double bond absorption of the enol form was displayed at 1609 cm^{-1}. In the ^1H NMR spectrum, the hydroxyl proton of the enol form appeared at δ 13.47. The methyl protons of the ester moiety of the major keto form were shown at δ 3.36 as a singlet, while the corresponding methyl protons in the minor keto form were found at δ 3.31. The methyl protons of the ester moiety of the enol form were shown at δ 3.25. A doublet of doublets (J = 5, 10.5 Hz) at δ 3.29 was assigned to the α proton of the β-keto ester moiety of the major keto form, while the corresponding proton in the minor keto form was shown at δ 3.46 as a doublet of doublets with coupling constants of 5 and 10.5 Hz. Three doublets at δ 1.55 (J = 7 Hz, major keto form), 1.06 (J = 7 Hz, enol form) and 1.01 (J = 7 Hz, minor keto form) were assigned to the methyl group attached to the cyclooctane ring. The existence of these three isomeric forms of **38** was confirmed by its ^{13}C NMR spectrum, in which the ketone carbonyl groups of the two keto forms were displayed at δ 213.1 (major) and 212.4 (minor), while the ester carbonyls of two keto and one enol forms were shown at δ 178.5, 173.8 and 170.5. In the high resolution mass spectrum, the molecular ion peak shown at m/z 198.12635 was consistent with the molecular formula $C_{11}H_{18}O_3$.



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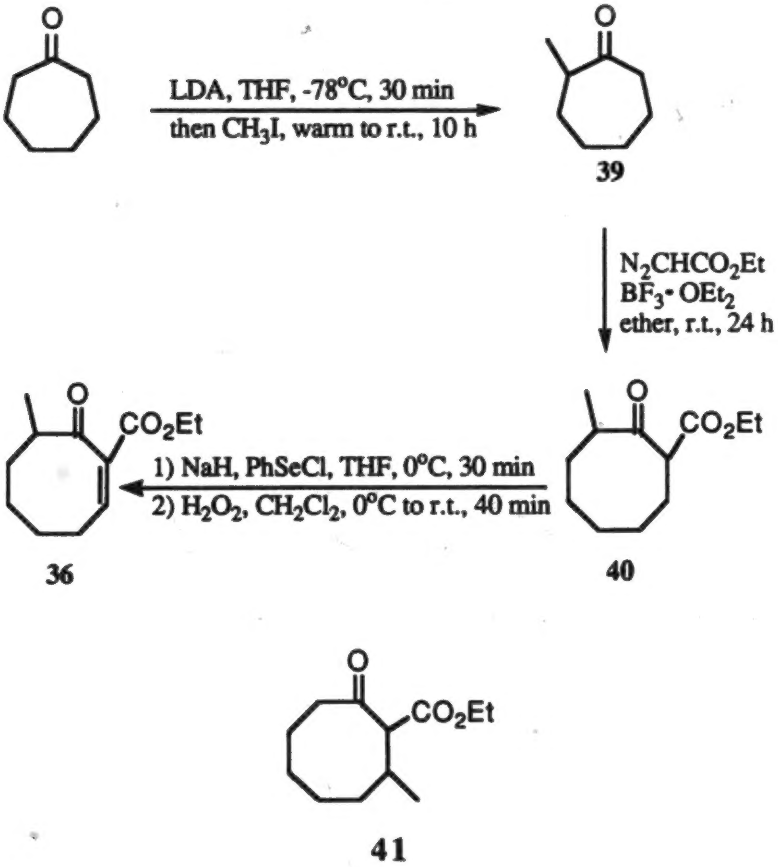
The conjugated double bond of enone **35** was constructed using a phenylselenenylation-oxidative elimination process. Compound **38** was first treated with sodium hydride and phenylselenenyl chloride in THF at

0°C for 30 min. The crude product without purification was immediately subjected to oxidation with hydrogen peroxide at 0°C in methylene chloride to give 2-carbomethoxy-8-methyl-2-cyclooctenone (**35**) in 86% yield over two steps. In the infrared spectrum, two carbonyl absorption bands were displayed at 1723 (ester) and 1695 cm^{-1} (ketone). The conjugated double bond absorption was shown at 1640 cm^{-1}. In the ^1H NMR spectrum, the methyl protons of the ester moiety appeared at δ 3.68 as a singlet, while the olefinic proton was shown as a triplet at δ 7.18 (J = 4.5 Hz). A doublet (J = 7 Hz) was observed for the α-methyl protons of the ketone moiety at δ 1.10. In the high resolution mass spectrum, enone **35** showed a molecular ion peak at m/z 196.11022 in agreement with the molecular formula $C_{11}H_{16}O_3$. The freshly prepared compound **35** existed exclusively in the keto form. This was confirmed by its ^{13}C NMR spectrum which displayed only one set of carbon signals with the ketone carbonyl signal at δ 211.0 and the ester carbonyl signal at δ 165.0. The olefinic carbons were found at δ 147.0 and 131.4.

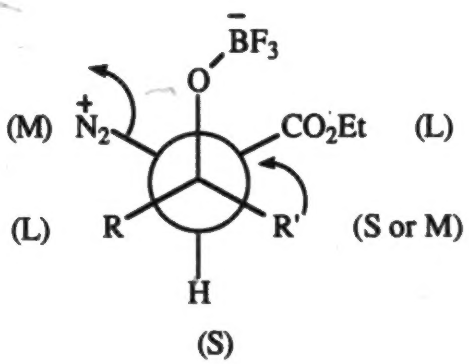
The preparation of 2-carbethoxy-8-methyl-2-cyclooctenone (**36**) is outlined in Scheme 6. 2-Methylcycloheptanone (**39**) was provided by Dr. J.B. Kim in our group. It was prepared from cycloheptanone in 70% yield by the same method described previously for the methylation of cyclooctanone.

2-Carbethoxy-8-methylcyclooctanone (**40**) was prepared using the Lewis acid catalyzed ring expansion reaction. Treatment of 2-methylcycloheptanone (**39**) with ethyl diazoacetate and boron trifluoride etherate in ether at room temperature for 24 h resulted in the formation of the desired β-keto ester **40** in 60% yield along with a minor amount of the isomeric β-keto ester **41** (38% yield).

Scheme 6. The preparation of enone **36**

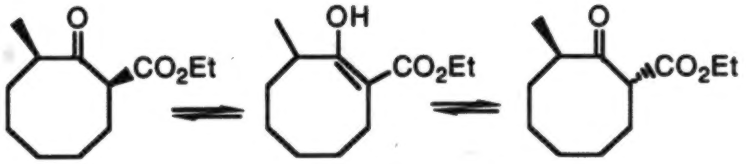

O
LDA, THF, -78°C, 30 min
then CH₃I, warm to r.t., 10 h
O
39
N₂CHCO₂Et
BF₃• OEt₂
ether, r.t., 24 h
O
CO₂Et
1) NaH, PhSeCl, THF, 0°C, 30 min
2) H₂O₂, CH₂Cl₂, 0°C to r.t., 40 min
O
CO₂Et
36
40
O
CO₂Et
41

This ring enlargement reaction, which has been extensively used , is highly reliable. It allows the direct formation of the β-keto ester system from a cyclic ketone. With symmetrical cycloalkanones, such as cyclohexanone and cycloheptanone, a single ring expansion product is usually formed in good yield. In cases of unsymmetrical cycloalkanones, the reaction is known to proceed with a high degree of regioselectivity. Studies on migratory aptitude indicated that, in general, the less substituted α-carbon migrates preferentially. The rationale behind this observation is that the conformation of the diazonium ion intermediate resulting from the initial addition of diazoacetate to the ketone carbonyl group determines the product formation of the reaction. The favored conformation **A** should be the one minimizing *gauche* repulsion. Then the preferred migration of the less bulky group (S or M) is predicted from conformation **A**. The regioselectivity is usually very good as demonstrated in the previous work of our group in the preparation of a variety of cyclic dienophiles, e.g. compounds **23-27** and **29**.[28b]



A

Unfortunately, this regioselectivity was not as high as we expected for the preparation of 2-carbethoxy-8-methylcyclooctanone (**40**). In the ring expansion reaction of 2-methylcycloheptanone (**39**), regioisomers **40** and **41** were produced in a ratio of 1.6:1 and in a combined yield of 98%. Although the desired compound **40** was formed as the major product as expected, the result was not highly satisfactory from a synthetic point of view.



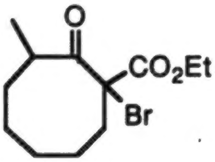
40

Compound **40** existed as a mixture of three isomeric forms shown below. The ratio of the keto forms to the enol form was 3.5:1, while the ratio of the two keto forms was 4:1. These ratios were obtained from the integration of the related peaks in the ^{1}H NMR spectrum. The signal of the hydroxyl group of the enol form was shown at δ 12.89. For the ester moiety, the methylene protons of enol form were shown at δ 4.19 as a quartet (J = 7 Hz) due to the coupling with the methyl protons which appeared at δ 1.28 as a triplet (J = 7 Hz). The methylene protons of the ester moiety of the major ketone form was shown at δ 4.12 as a multiplet, while the adjacent methyl protons were shown at δ 1.21 as a triplet (J= 7 Hz). The allylic methyl protons of the enol form were observed at δ 1.12 as a doublet (J = 7 Hz). The α–methyl protons of the major keto form were shown as a doublet at δ 1.11 (J = 7 Hz). A weak signal at δ 0.95 (d, J = 7 Hz) was assigned to the α-methyl group of the minor keto form. The existence of these three isomeric forms was confirmed by the ^{13}C NMR spectrum in which the ketone carbonyl signals of the keto forms were shown at δ 215.0 and 213.7, and the ester carbonyl signals were displayed at δ 177.9, 170.24 and 170.15. In the infrared spectrum, three carbonyl absorption bands were displayed at 1747 (esters of keto forms), 1708 (ketones of keto forms), and 1638 cm^{-1} (ester of the enol form). The olefinic double bond of the enol form was shown at 1609 cm^{-1}. In the high resolution mass spectrum, compound **40** showed the molecular ion peak at m/z 212.14087 which was consistent with the molecular formula $C_{12}H_{20}O_3$.

The structure of the minor isomer **41** was also established spectroscopically. In the infrared spectrum, two carbonyl bands were displayed at 1745 (ester) and 1705 cm^{-1} (ketone). In the ^1H NMR spectrum, the methylene protons of the ester moiety were shown at δ 4.10 as a multiplet, while the adjacent methyl protons were shown at δ 1.20 as a triplet (J = 7 Hz). The β-methyl group was displayed at δ 0.95 as a doublet. In the ^{13}C NMR spectrum, a pair of signals at δ 211.0 and 169.4 were assigned to the two carbonyl groups. The high resolution mass spectrum showed the molecular ion peak at m/z 212.14058 in accordance with the molecular formula $C_{12}H_{20}O_3$. These spectral data also suggested that compound **41** existed exclusively in the keto form as a single diastereomer. Its stereochemistry, however, could not be assigned with certainty.

A phenylselenenylation-oxidative elimination reaction sequence was also applied to keto ester **40** for the installation of the conjugated carbon-carbon double bond. Under conditions virtually identical to those described previously for the transformation of **38** to **35**, the desired enone ester **36** was isolated in 85% yield. This compound showed, in the infrared spectrum, two carbonyl absorption bands at 1720 (ester) and 1696 cm^{-1} (ketone). The conjugated double bond was shown at 1639 cm^{-1}. In the ^1H NMR spectrum, the distinct vinylic proton was displayed as a triplet (J = 4.5 Hz) at δ 7.18. The α-proton of the ketone carbonyl was shown as a multiplet at δ 2.60. For the ester moiety, the methylene protons were displayed at δ 4.27 as a multiplet coupled to the methyl triplet at δ 1.23 with a coupled constant of 7 Hz. In the high resolution mass spectrum, a molecular ion peak was observed at m/z 210.12554 in agreement with the molecular formula of $C_{12}H_{18}O_3$.

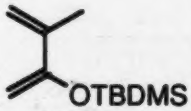
Attempts were also made to effect the formation of the double bond using the bromination-dehydrobromination protocol.[39] This process has been used successfully in our laboratory on several occasions with similar compounds. In the present case, however, treatment of keto ester **40** with *N*-bromosuccinimide in carbon tetrachloride in the dark gave invariably a complex mixture of products without the apparent formation of the desired compound **42**.



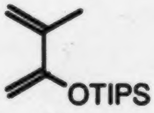
42

II. Diels-Alder reactions of 2-carbomethoxy-8-methyl-2-cyclooctenone (35) and 2-carbethoxy-8-methyl-2-cyclooctenone (36)

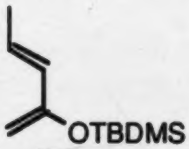
All the dienes used in this study were commercially available except for those having a trialkylsilyloxy group as a substituent at the 2-position (**43, 44, 45** and **46**). Diene **43**, a known compound, was prepared from 3-methyl-3-butenone by a known procedure,[40] using *tert*-butyldimethylsilyl chloride as a reagent. Dienes **44, 45** and **46** were prepared from the appropriately substituted methyl vinyl ketone with the required trialkylsilyl chloride as a reagent using the same preparative procedure as **43**. The crude product was purified by vacuum distillation. Cyclopentadiene was obtained from the pyrolysis of the commercially available dimer.



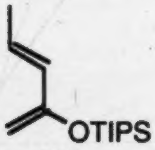
43



44



45



46

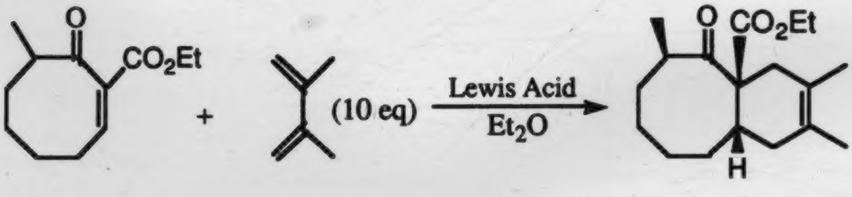
Based on the results of the previous studies on the Diels-Alder chemistry of 2-carbethoxy-2-cyclooctenone (**33**) and a number of related dienophiles in our laboratory, several Lewis acids (ferric chloride, tin(IV) chloride, zinc chloride and boron trifluoride etherate) were chosen as the catalysts for the current studies on the Diels-Alder reaction of enones **35** and **36**.

The procedures for the Diels-Alder reactions catalyzed by ferric chloride, tin(IV) chloride and boron trifluoride etherate were very straightforward. The Lewis acid was simply added to an ethereal solution of the dienophile and diene. The zinc chloride catalyzed reactions were carried out in a somewhat different manner. Zinc chloride was flame fused before being dissolved in ether. An ethereal solution of the dienophile was then added. After stirring for 0.5 h (allowing for complex formation), diene was introduced. All reactions were monitored with TLC and, upon complete consumption of the dienophile, the reaction was quenched and neutralized by addition of saturated aqueous sodium bicarbonate solution.

In order to determine the most suitable conditions, all four Lewis acids were explored for the Diels-Alder reaction of enone **36** and 2,3-dimethyl-1,3-butadiene. The choice of reaction conditions was based on the previous studies of the Diels-Alder reaction of enone **33** (Entry 1, Table 2). In the reaction of enone **33** and isoprene at -20°C, ferric chloride and tin(IV) chloride gave good results. On the other hand, the reactions catalyzed by zinc chloride and boron trifluoride etherate were pretty sluggish even at 0°C over a long reaction time. For the ferric chloride catalyzed reaction, the reaction was rapid (20 min) even at -20°C. The isolated yield of 84%, although quite satisfactory from a synthetic point of view, still left some room for improvement. Since Lewis acid accelerates both the Diels-Alder reaction and the polymerization of diene, we decided to lower the reaction temperature in order to slow down the rate of polymerization. In order to make parallel comparison, the tin(IV) chloride catalyzed reaction was also carried out under the same conditions. Due to their low efficiency at 0°C, we decided to carried out the zinc chloride and boron trifluoride etherate catalyzed reactions at room temperature so as to improve the yields. The results are summarized in Table 3.

As indicated in Table 3, except for the boron trifluoride etherate catalyzed reaction, the yields were greatly improved over those obtained in the previous investigation with **33**. Moreover, a single stereoisomer was produced. For the boron trifluoride etherate catalyzed reaction, however, the result was inferior. No reaction took place after 52 h, and the dienophile **36** was recovered quantitatively. In terms of the rate of reaction, the ferric chloride catalyzed reaction occurred most rapidly (30 min at -40°C), followed by the one catalyzed by tin(IV) chloride (17 h at -40°C). Zinc chloride was shown to be the least effective catalyst of the three. At room temperature and with two equivalents of the catalyst, it took more than four days for the reaction to complete.

Table 3. Lewis acid catalyzed Diels-Alder reactions of enone **36** and 2,3-dimethyl-1,3-butadiene

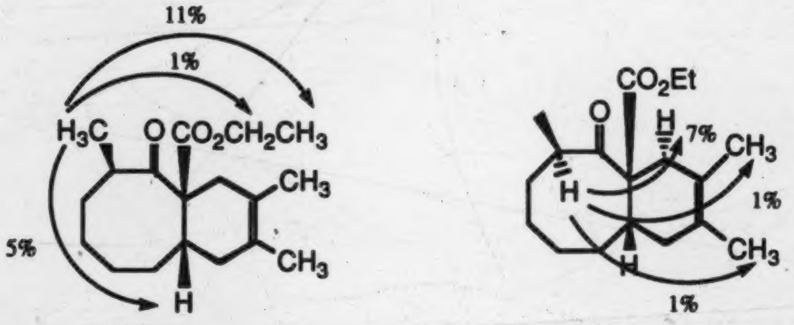


36 **47**

Time (h)	Temp. (°C)	Lewis acid	Yield (%)
0.5	-40	$FeCl_3$ (1 eq)	96
17	-40	$SnCl_4$ (1 eq)	98
101	R.T.	$ZnCl_2$ (2 eq)	85
52	R.T.	$BF_3 \cdot OEt_2$ (1 eq)	0

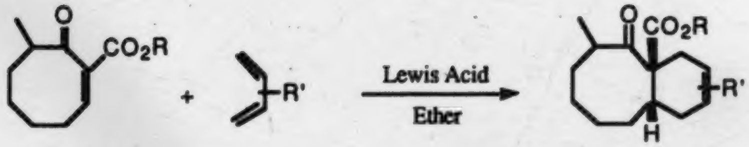
The structure of adduct **47** was deduced as follows. The infrared spectrum displayed two carbonyl absorption bands at 1737 (ester) and 1695 cm^{-1} (ketone). The high resolution mass spectrum showed a molecular ion peak at m/z 292.20349, corresponding to the molecular formula $C_{18}H_{28}O_3$. The ^{13}C NMR APT spectrum of **47** displayed only one set of signals, including two carbonyl signals at δ 216.8 (ketone) and 172.2 (ester) and two olefinic signals at δ 124.0 and 121.7, indicating the presence of a single compound. The assignment of the ^1H NMR spectrum of **47** was assisted by extensive proton spin decoupling and COSY experiments. The two vinylic methyl groups appeared as broad singlets at δ 1.63 and 1.54, respectively. The methylene protons of the ester moiety were shown as a multiplet at δ 4.15 . The adjacent methyl group was displayed at δ 1.21 as a triplet (J = 7 Hz). The α-methine proton of the ketone moiety was shown at δ 3.25 as a multiplet. The allylic methylene protons at C-12 were displayed at δ 2.59 as a singlet, while the other allylic methylene protons at C-9 were shown at δ 2.66 as a multiplet. The stereochemistry of the adduct was determined with the aid of NOE experiments. The NOE results are shown in Fig. 1. It is clear from these results that the diene was added from the opposite side of the α-methyl of the ketone (the proton face), and the adduct was formed via the transition state in which the secondary orbital interaction occurred between the π system of the diene and the carbonyl of the ester (*endo*-to-ester).

Fig. 1 The NOE results of adduct **47**

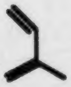
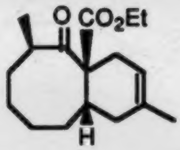
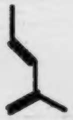
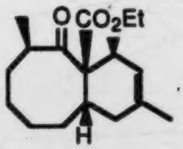
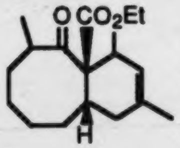
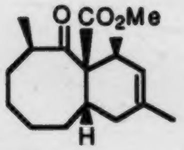
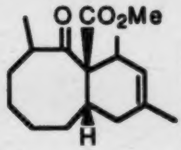
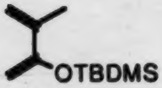
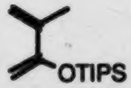
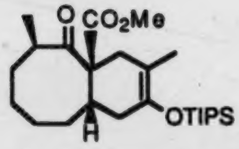


Based on the above results obtained using various Lewis acid catalysts, ferric chloride was considered to be most effective. Consequently, this Lewis acid was chosen for further investigation on the general scope of the Diels-Alder reaction of the enones **35** and **36**. The results are summarized in Table 4.

Table 4. Lewis acid catalyzed Diels-Alder reactions of enones **35** and **36**



35 R = Me
36 R = Et

Entry	Diene	Time (h)	Temp. (°C)	Product(s)	Lewis Acid	Yield (%)
1	 (10 eq)	0.5	-40	 **48**	FeCl$_3$ (1 eq)	95
2	 (10 eq)	0.5 0.5 0.5	-40 -50 -78	 **49** (4 : 1) **50** 	FeCl$_3$ (1 eq)	75 80 77
		0.5 24	-78 -78	 **51** (4 : 1) **52** 	FeCl$_3$ (1 eq) SnCl$_4$ (1 eq)	82 80
3	 (10 eq)			Unstable		
4[1]	 (2 eq)	4	-78	 **53**	SnCl$_4$ (1 eq)	90

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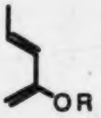
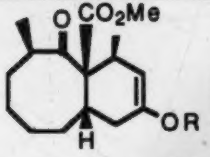
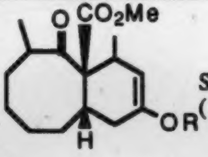
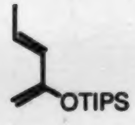
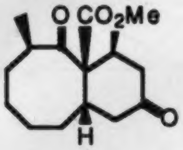
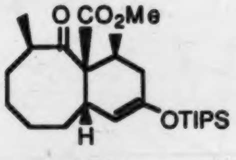
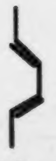
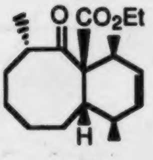
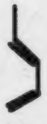
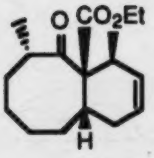
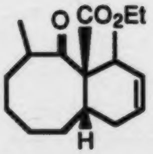
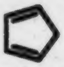
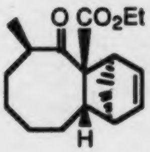
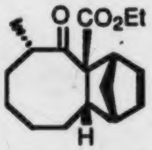
[1] In this reaction, the diene was added to the solution of the complex of enone **35** and the Lewis acid.

Table 4 (cont.)

Entry	Diene	Time (h)	Temp. (°C)	Product	Cata.	Yield (%)
5[1]	 (10 eq), R = TBDMS	1	-78	 **54** (2 : 1)  **55**	$SnCl_4$ (1 eq)	89
6[1]	 (2 eq)	1	-78	 **57**	$SnCl_4$ (1 eq)	98
				 **56**		Trace
7	 (10 eq)	5.5 2	-40 -20	 **58**	$FeCl_3$ (1 eq)	92 68
8	 (10 eq)	0.4 0.5	-40 -78	 **59** (4 : 1)  **60**	$FeCl_3$ (1 eq)	68 92
9	 (10 eq)			 **61**  **62**		
		1	-78	2 : 1	$FeCl_3$ (1 eq)	76
		78	0 → 20	1 : 1	$ZnCl_2$ (2 eq)	91

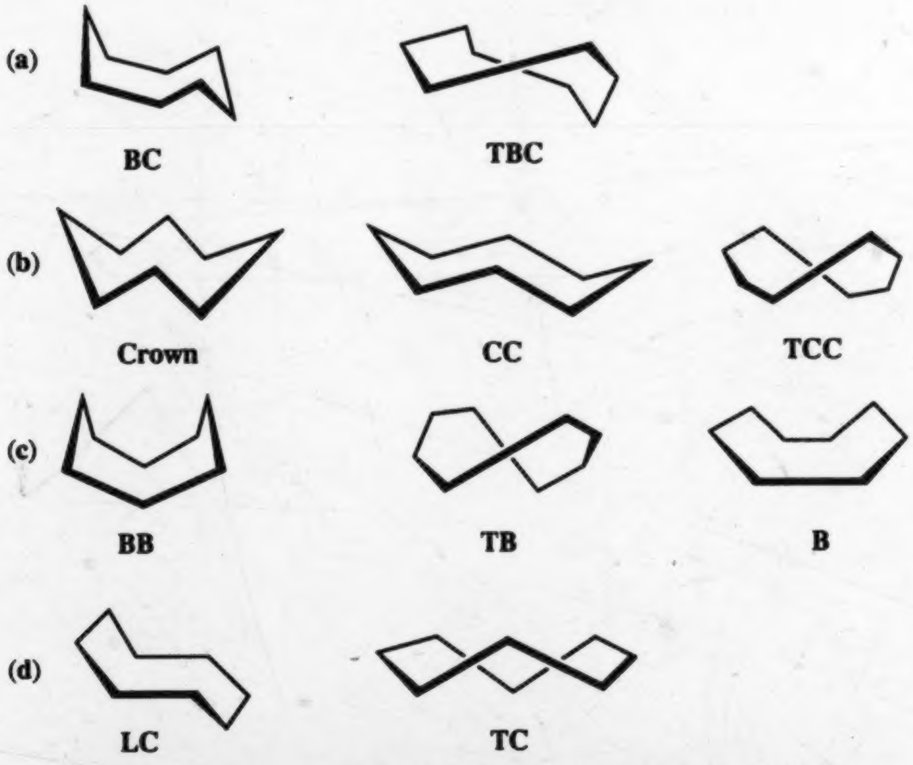
An examination of Table 4 reveals that all the Diels-Alder reactions of cyclooctenones **35** and **36** followed the *ortho*- and *para*-rule without exception. In case of the 1-substituted diene (Entry 8), compounds **59** and **60** were obtained as predicted by the *ortho*-rule. In the case of 2-substituted diene (Entry 1), *para*-adduct **48** was obtained as the only regioisomer. In reaction with the 1,3-disubstituted butadiene (Entries 2, 5 and 6), the *ortho*- and *para*-rule worked in a complementary fashion so that in the Diels-Alder adduct, one substituent of the diene was adjacent to the ester group of enones **35** and **36** (*ortho* position), the other one was in the *para* relationship with the ester group. In case of the unsymmetrical 2,3-disubstituted diene (Entry 4), the more powerful electron-donating group played the role in controlling regioselectivity. Thus, for compound **53**, the triisopropylsilyloxy group, a better electron-donating group than the methyl group, was at the *para* position relative to the ester group.

Although the regioselectivity of the Diels-Alder reaction followed strictly the empirical rules (*ortho* and *para*), the stereoselectivity of the reaction was not very predictable. In general, the stereochemistry of the adduct of Diels-Alder reaction is controlled by the electronic and/or steric effect. Because there is a methyl group at the α position of the ketone moiety of the dienophile, the presence of this stereocenter introduces a new aspect of stereoselectivity, *i.e.*, the facial selectivity. The diene might add to the enone from either the same face as the methyl group (the methyl face) or the face opposite to the methyl group (the proton face) which is assumed to be the less hindered face. Both phenomena were observed in the previous studies.[28b] At the same time, due to the presence of an ester group as an additional activating group, the secondary orbital interaction might occur between the π bond of diene and either the carbonyl group of the ketone, which generates *endo*-to-ketone adduct, or the carbonyl group of the ester, from which the *endo*-to-ester adduct would be obtained.

As indicated in Table 4, except for the case of cyclopentadiene (Entry 9), all the adducts were obtained via *endo*-to-ester transition state. The Diels-Alder reaction of cyclopentadiene (Entry 9) was a special case due to its methylene group, but the major product was still the *endo*-to-ester adduct **61**. Interestingly, in terms of facial selectivity, the Diels-Alder adducts in this study fall into two groups based on the diene used. When the C-2 position was substituted, the dienes would add to the dienophiles from the proton face (for examples, Entries 1, 2, 4, 5 and 6), and when there was no substituent on C-2, the dienes would added to the dienophile from the methyl face (Entries 7 and 8). Unfortunately, the reason why the C-2 unsubstituted dienes preferred to approach dienophiles **35** or **36** from the methyl face remains unclear, and further investigation is warranted. It should also be pointed out that the Diels-Alder additions of (*E*)-2-(*t*-butyldimethylsilyloxy)- and (*E*)-2-(triisopropylsilyloxy)-1,3-pentadiene to enone **35** form a integral part of a project directed towards the total synthesis of sesquiterpenes neolemnane and its acetate.[41] Detailed studies of these reactions are to be found in Chapter 2 of this thesis. Only selected results are included in Table 4, Entries 5 and 6.

During the last two decades, extensive investigations devoted to the eight-membered cyclic system have been reported. Among these studies, more and more interest has been focused on rings that contain one or more planar group of atoms with unsaturated bonds (a carbon-carbon double bond, aromatic ring, etc.). In examination of the conformers of unsubstituted cyclooctane, ten conformations can be adopted, which constitute four groups (Figure 2).[42]

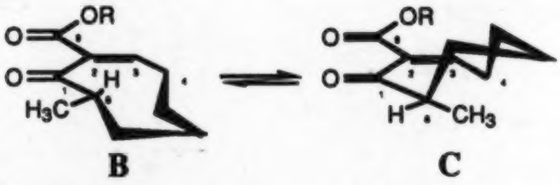
Fig. 2. The possible conformations of cyclooctane



(a) The boat-chair (BC) group: boat-chair (BC) and twist-boat-chair (TBC); (b) The crown group: crown, chair-chair (CC), and twist-chair-chair (TCC); (c) The boat group: boat-boat (BB), twist-boat (TB), and boat (B); (d) The chair group: long-chair (LC), and twist-chair (TC).

Some conclusions have been drawn from these investigations. The BC form is the preferred conformation among all the conformations of the unsubstituted eight-membered ring. The introduction of planar fragments into the *exo* or *endo* positions of the cyclooctane ring affects the stabilization of the conformation of the eight-membered ring system in different ways. When a single planar fragment is introduced into an eight-membered ring system, no substantial change will take place in their conformational behaviors, but introduction of two planar fragments will result in a lot of changes in the ring conformations of cyclooctanone. The most favorable conformation will be determined by the relationship of the two planar fragments.

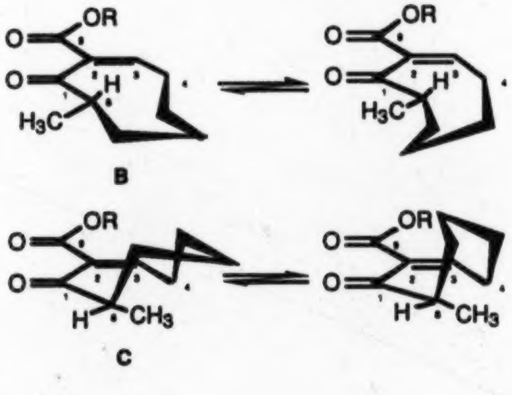
Figure 3. Two possible conformations of enones **35** and **36**



In case of 2-carbalkoxy-8-methyl-2-cyclooctenones **35** and **36**, it is clear, based on the above discussion, that the conjugated enone portion must play a very important role in the conformational behavior of the eight-membered ring system. Two planar fragments were introduced into the eight-membered ring system and formed a conjugated system. One was the carbonyl group which was at an *exo* position of the ring while the other was the double bond which was in an *endo* position. The introduction of the carbonyl group, an *exo*-planar fragment, into the α-position of the double bond, an *endo*-planar fragment, caused it to adopt a coplanar configuration. The ester group, although it was not considered as a planar fragment of this ring system according to the previous concept, must have a strong influence on the conformation of the eight-membered ring system because the carbonyl of the ester group was also in conjugation with the α, β-unsaturated ketone moiety of the ring and stayed in the same plane in order to form the most stable molecular conformation. Among all the possible conformations of the carbalkoxycyclooctenones **35** and **36**, two conformations were very attractive (Figure. 3).

In both conformations, in order to allow for maximum conjugation, the carbon atoms, C-1, C-2, C-3, C-4, C-8 and C-9 must be in the same plane. The remainder of the ring may lie either above the plane or below the plane. Furthermore, due to the high mobility and flexibility of the eight-membered ring, both conformations **B** and **C** might exist in their own conformational equilibrium as shown in Figure 4.

Fig. 4 The conformational equilibrium of **B** and **C**



Conformation **B** can be used to explain the addition in which the diene added from the proton face of the dienophile, while the conformation **C** can be used to explain the addition in which the diene added to dienophile from the methyl face. In conformation **B**, in order to keep the carbon atoms of the conjugated system co-planar while reducing the ring strain, the α-methyl group of the ketone carbonyl, which is in the *pseudo*-equatorial position, has to be located in the plane of the conjugated system. This causes an unfavorable steric interaction between the carbonyl group and the methyl group, thus allowing for **B** → **C**. In conformation **C**, for the same reason, the α-proton of the ketone has to be in the plane of the conjugated system, then a strong transannular repulsion between the *pseudo*-axial α-methyl group and one of allylic hydrogens would result, thus allowing for **C** → **B**.

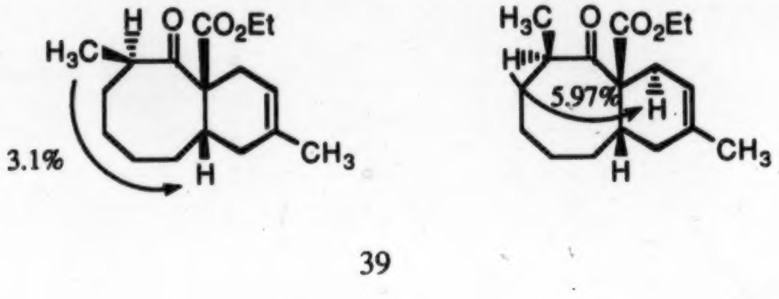
From the experimental results, it seems that the facial selectivity of the Diels-Alder reaction involving enones **35** and **36** was controlled by the ring conformation of the eight-membered ring system with conformation **B** being preferred. However, the selectivity was not totally consistent. This phenomenon is indicative of an equilibrium between the two conformations **B** and **C** under the reaction conditions. Unfortunately, up to now, it remains unclear as to how the presence of the planar fragments and the conjugated system affects the conformation of the eight-membered ring.

In terms of *endo* selectivity, the *endo*-to-ester products were obtained either exclusively or as the major product (Entry 9) in all reactions. According to the above discussion on the eight-membered ring conformation, it is quite likely that this selectivity arose mainly from the steric effect. As indicated in Figures 3 and 4, the *endo*-to-ketone addition was blocked by the saturated portion of the eight-membered ring system. Thus, if the addition occurred in an *endo*-to-ketone manner, the high steric interaction between the incoming diene and the trimethylene portion of the dienophile would offset the stabilizing effect resulting from the secondary orbital overlap involving the ketone carbonyl and the diene. On the other hand, with the exception of cyclopentadiene (Entry 9) which gave poor *endo* selectivity, there is no such steric repulsion in the *endo*-to-ester transition state, while the diene can also effectively overlap with the carbonyl of the ester. The transition state of *endo*-to-ketone is thus likely to be much less stable than that of *endo*-to-ester. Based on these considerations, it is expected that the stereoselectivity can be controlled by adjusting the size of the substituent on the diene. This expectation was realized experimentally in connection with our studies towards the total synthesis of neolemnane (Chapter 2).

The Diels-Alder reaction of cyclopentadiene presents itself as a special case. As indicated in Table 4 (Entry 9), a mixture of two diastereomers was obtained. One isomer **61** was produced via the *endo*-to-ester addition from the proton face, and the other **62** involving *endo*-to-ketone addition from the methyl face. The ratio of these two isomers (**61** : **62**) varied considerably under different reaction conditions. In the ferric chloride catalyzed reaction, the ratio was 2 : 1, while in the zinc chloride catalyzed reaction, a 1:1 mixture was obtained. The lack of stereoselectivity of this Diels-Alder reaction could be the result of the unique structure of cyclopentadiene. Due to its cyclic structure, the steric interaction between the methylene group of cyclopentadiene and the saturated ring portion of the dienophile was compatible with that between the conjugated moiety of diene and the same ring portion of the dienophile. Thus, the activating energy difference between the *endo*-to-ester transition state and the *endo*-to-ketone transition state was not big enough to allow for good selectivity. Furthermore, the stereoselectivity of the reaction is also strongly influenced by the complexation of Lewis acid and dienophile, reaction conditions, as well as other electronic and steric effects.

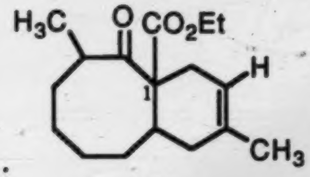
In the Diels-Alder reaction of enone **36** and isoprene (Entry 1 in Table 4) catalyzed by ferric chloride, compound **48** was obtained exclusively in 95% yield. The infrared spectrum of the adduct **48** showed two carbonyl absorptions at 1737 (ester) and 1695 cm^{-1} (ketone). The high resolution mass spectrum displayed the molecular ion peak at m/z 278.18771 corresponding to the molecular formula of $C_{17}H_{26}O_3$. The ^{13}C NMR (APT) spectrum showed only one set of carbon signals, indicating that a single adduct was formed. Two carbonyl signals were shown at δ 216.9 (ketone) and 172.2 (ester). The vinylic carbon signals were displayed at δ 132.4 (in phase) and 116.9 (antiphase). The ^1H NMR spectrum displayed the olefinic proton signal as a multiplet at δ 5.33. The four allylic protons appeared in the region of δ 2.82 - 2.50. The methylene protons of the ester moiety were shown at δ 4.17 as a multiplet. The adjacent methyl protons were found at δ 1.23 as a triplet (J = 7 Hz). Two other methyl signals were also observed: a singlet at δ 1.60 for the vinylic methyl group and a doublet (J = 6.5 Hz) at δ 1.04 for the methyl group next to the ketone. The stereochemistry of the adduct **48** was

Fig. 5. The NOE results of compound **48**

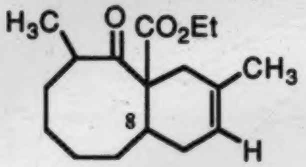


deduced from the results of the NOE experiments shown in Figure 5, indicating that the diene was added from the proton face of enone **36**.

Because the *anti-para* Diels-Alder adduct was produced in some cases in the previous studies of our group, it was deemed necessary to confirm the regiochemistry of the adduct **48**. The determination of the regiochemistry of **48** was carried out both chemically (photooxidation reaction) and spectroscopically (INEPT). In the INEPT experiment, when the vinylic proton of **48** at δ 5.30 was irradiated, the signal of the ring junction carbon C-1, which was at δ 63.3 and in phase in the ^{13}C NMR APT spectrum, was observed in the corresponding INEPT ^{13}C NMR spectrum of **48.** With the hypothetical *anti-para* adduct **65**, irradiation of the vinylic proton should result in the display of the antiphase signal of C-8 in the corresponding ^{13}C NMR APT spectrum, and this was not observed.



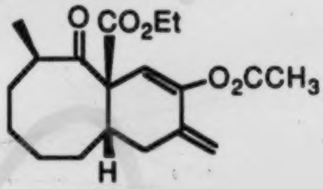
48



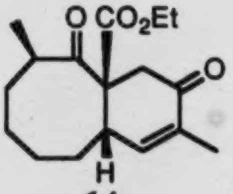
65

In the photooxidation reaction of compound **48**, oxygen was gently bubbled through a carbon tetrachloride solution of compound **48**, pyridine, 4-(*N,N*-dimethylamino)pyridine (DMAP), 5,10,15,20-tetraphenyl-21*H*, 23*H*-porphine (TPP) and acetic anhydride. This solution was irradiated with two two hundred watt tungsten bulbs for 35 h. After turning off the light, oxygen was allowed to pass through the reaction mixture for an additional period of 19 h. Two products **63** and **64** were obtained. The structure of these products was deduced by the following spectral data.

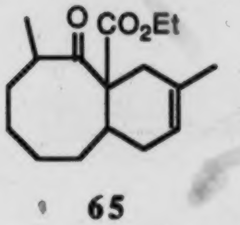
The infrared spectrum of **64** displayed three carbonyl absorption bands at 1738 (ester), 1698 (ketone) and 1682 cm^{-1} (conjugated ketone). The high resolution mass spectrum showed the molecular ion peak at m/z 292.16791 which was consistent with the molecular formula $C_{17}H_{24}O_4$. In the ^{13}C NMR (APT) spectrum, three carbonyl signals were displayed at δ 213.0, 195.2 and 171.1, while two vinylic carbon signals appeared at δ 148.1 and 133.3. In the ^1H NMR spectrum, the vinylic proton signal was displayed at δ 6.60 as a quartet of doublets (J = 1, 5.5 Hz). This finding confirmed the depicted regiochemistry of adduct **48**. The observed multiplicity of the vinyl proton indicated that it was coupled with both the ring junction proton (J = 5.5 Hz) and the vinylic methyl protons (J = 1 Hz). If the *anti-para* adduct **65** was obtained, then the product of its photooxidation would be expected to be **66**. Theoretically, the multiplicity of its vinyl proton signal could be either a broad singlet or a quartet with a very small coupling constant arising from coupling with the vinylic methyl group. Based on the information gathered from photooxidation reaction and the INEPT experiment, the regiochemistry of adduct **48** was unambiguously deduced.



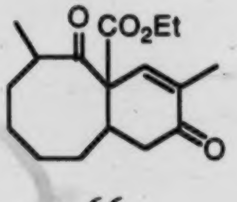
63



64



65



66

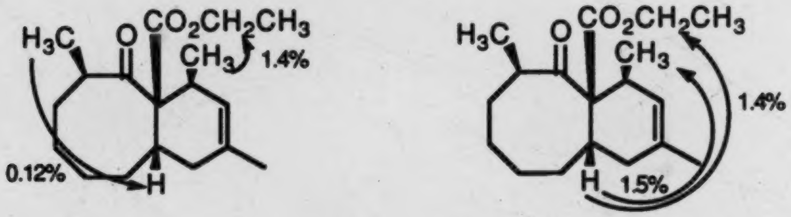
In the Diels-Alder reaction with 2-methyl-1,3-pentadiene (Entry 2), enones **35** and **36** were both used as dienophiles. Each gave an inseparable mixture of two diastereomeric adducts in a ratio of 4 : 1. In order to improve the stereoselectivity, the reaction was carried out under various conditions, however the results remained unchanged. Two carbonyl bands were found at 1723 (ester) and 1696 cm^{-1} (ketone) in the infrared spectrum of the mixture. The molecular ion peak at m/z 292.20374 shown in its high resolution mass spectrum indicated the molecular formula of $C_{18}H_{28}O_3$. For the major isomer **49** obtained from enone **36**, the ^{13}C NMR APT spectrum displayed two carbonyl signals at δ 214.3 (ketone) and 173.5 (ester) and two olefinic carbon signals at δ 132.2 and 125.0. The vinylic proton was found as a multiplet at δ 5.08 in the ^1H NMR spectrum. The methylene protons of the ester moiety appeared at δ 4.15 as a multiplet, while the adjacent methyl group was observed at δ 1.20 as a triplet (J = 7 Hz). The methyl group at C-12 was shown as a doublet at δ 0.88 (J = 7.5 Hz) and the adjacent allylic proton appeared at δ 2.85 as a multiplet. The other two allylic protons at C-9 were displayed as a pair of doublets of doublets at δ 2.29 (J = 6, 18 Hz) and 2.05 (J = 6, 18 Hz). The vinylic methyl group was observed at δ 1.60 as a singlet. The remaining methyl group was shown at δ 0.95 as a doublet (J = 6.5 Hz). The ring junction proton was displayed at δ 2.60 as a multiplet. The NOE experimental results (Fig. 6) indicated the stereochemistry of the major isomer as shown. Because it was not possible to separate the two isomers **49** and **50**, the stereochemistry of the minor isomer **50** could not be deduced using the same technique.

For the mixture of **51** and **52** obtained from the Diels-Alder reaction of enone **35**, two carbonyl bands were displayed at 1733 (ester) and 1699 cm^{-1} (ketone) in the infrared spectrum. The molecular ion peak in accord with the molecular formula of $C_{17}H_{26}O_3$ was found at m/z 278.18799 in the high resolution mass spectrum. For the major isomer **51**, the ^{13}C NMR (APT) spectrum displayed two carbonyl signals at δ 214.2 (ketone) and 174.1 (ester), while two olefinic carbon signals were found at δ 132.2 and 125.0. In the ^{1}H NMR spectrum, the vinylic proton appeared as a multiplet at δ 5.13. The methyl group of the ester moiety was displayed at δ 3.72 as a sharp singlet. A broad singlet at δ 1.67 was assigned to the vinylic methyl group. The methyl group at C-12 was shown as a doublet at δ 0.90 with a coupling constant of 7 Hz, while the adjacent methine proton was shown at δ 2.84 as a multiplet. The other two allylic protons were shown at δ 2.30 (dd, J = 10.5, 19 Hz) and 2.07 (dd, J = 8, 19 Hz). The methyl group next to the ketone appeared at δ 0.98 as a doublet with a coupling constant of 7 Hz, while the adjacent methine proton was shown as a multiplet at δ 2.50. The stereochemistry of adduct **51** was deduced from the results of NOE experiments shown in Figure 6.

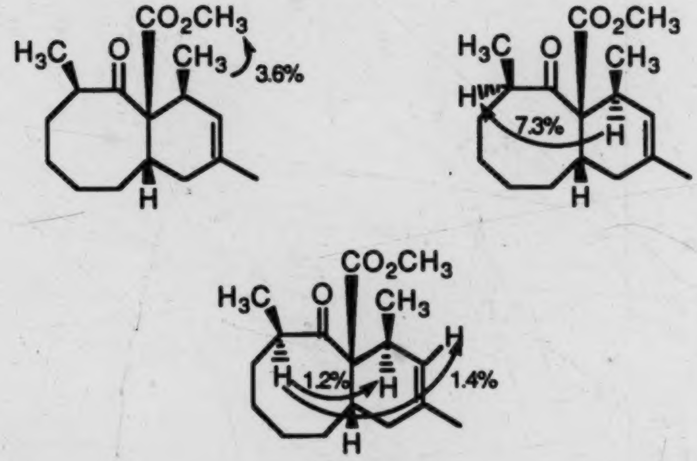
In order to expand the scope of the Diels-Alder process, the dienes **43-46** each with a trialkylsilyloxy substituent were examined, whereby more functionality would be introduced to the Diels-Alder adduct. Surprisingly, the adducts expected from the reactions of diene **43** with enones **35** and **36** (Entry 3, Table 4) were found to be highly unstable and could not be isolated and characterized. Decomposition occurred in the NMR sample tube with C_6D_6 as a solvent in 20 min to give a complicated mixture. Even at -22°C in the freezer, extensive decomposition was observed within 24 h.

Figure. 6 The NOE results of compounds **49** and **51**

Compound **49**



Compound **51**



In order to circumvent the problem, another trialkylsilyloxy group was used. To our delight, the Diels-Alder reaction of diene **44** and enone **35** (Entry 4) carried out by adding the diene to the solution of the preformed complex of the enone and Lewis acid, gave a stable adduct **53** which could be purified by flash chromatography. As expected, the diene approached the dienophile from the proton face. Under tin(IV) chloride catalysis, this Diels-Alder reaction produced the product **53** in 90% yield.

In its infrared spectrum, two carbonyl bands were displayed at 1744 (ester) and 1696 cm^{-1} (ketone), while an olefinic double bond absorption appeared at 1658 cm^{-1}. The ^{13}C NMR (APT) spectrum displayed two carbonyl signals at δ 215.1 and 172.1 and two olefinic carbon signals at δ 142.2 and 106.8. In the ^{1}H NMR spectrum, the ester methyl group was shown as a singlet at δ 3.40. Two broad doublets at δ 3.05 (J = 18 Hz) and 1.73 (J = 18 Hz) were assigned to the allylic protons at C-9. The signals of the other allylic protons at C-12 appeared at δ 2.83 (d, J = 18 Hz) and 2.64 (d, J = 18 Hz). The methyl group adjacent to the ketone was shown at δ 0.97 as a doublet (J = 7.5 Hz). In the high resolution mass spectrum, the molecular ion peak at m/z 436.30084 confirmed its composition of $C_{25}H_{44}O_4Si$. The regiochemistry was elucidated with the aid of extensive proton spin decoupling experiments. The stereochemistry was readily determined by the NOE experiments (Fig. 7).

Figure 7 The NOE result of compound **53**

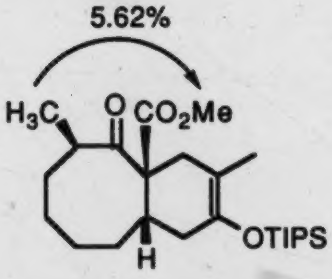
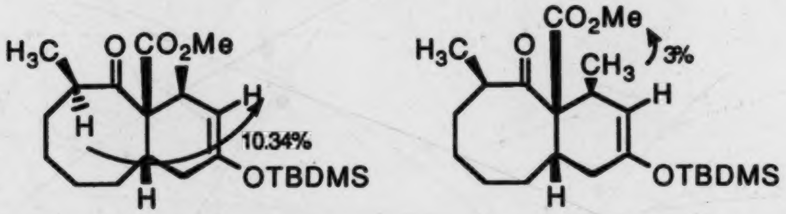


Table 4 also contains the best results obtained from an investigation on the Diels-Alder addition of enone **35** to dienes **45** and **46** in connection with a projected total synthesis of neolemnane. The preliminary studies leading to these results will be detailed in the next chapter.

The reaction of enone **35** and diene **45** was carried out as follows. A ethereal solution of **35** and tin(V) chloride was stirred at -78°C for 20 min to allow for complex formation. The diene **45** was then added at -78°C. After 4 h, an inseparable mixture of two stereoisomers **54** and **55** was obtained in 89% yield in a ratio of 2 : 1. In the infrared spectrum, two carbonyl absorption bands were shown at 1694 (ketone) and 1730 cm^{-1} (ester). In the high resolution mass spectrum, the molecular ion peak was found at m/z 394.25318 which was consistent with the molecular formula $C_{22}H_{30}O_4Si$. For the major isomer **54**, the ^1H NMR spectrum displayed a broad singlet at δ 4.72 for the vinylic proton. The methyl ester moiety was displayed at δ 3.32 as a sharp singlet. The allylic methine proton appeared at δ 3.15 as a multiplet, and the adjacent methyl was found at δ 1.17 as a doublet (J = 7.5 Hz). The allylic methylene protons on C-9 were observed at δ 2.30 (dddd, J = 1.5, 3, 9.5, 18 Hz) and 2.10 (dddd, J = 1.5, 3, 7.5, 18 Hz). In addition, a multiplet at δ 2.95 and a doublet at δ 1.27 (J = 7 Hz) could be attributed to the α-proton of the ketone and its neighboring methyl group, respectively. For the minor isomer, the broad singlet at δ 4.78 was assigned to the vinylic proton and the methyl protons of the ester moiety were shown at δ 3.39 as a sharp singlet. The allylic proton which coupled with a methyl group was shown at δ 2.83 as a multiplet. The α-proton of the ketone was displayed at δ 2.53 as a multiplet due in part to coupling with the methyl protons shown at δ 1.15 as a doublet (J = 7.5 Hz). The ^{13}C NMR (APT) spectrum of the mixture displayed two intense signals at δ 211.8 and 173.4 and two weak signals at δ 215.3 and 171.8 for a total of four carbonyl groups present in the two isomers. The two vinyl carbons of the major isomer appeared at δ 148.6 and 107.7, while one of the minor's was shown at δ 108.2. The methyl groups of the ester moieties of the two isomers were displayed at δ 51.4 (major) and 51.2 (minor). The stereochemistry of the major isomer was determined by the NOE experiment. The results are shown in Figure 8. The stereochemistry of the minor isomer remains unclear due to the difficulties in carrying out NOE experiments on the minor set of signals.

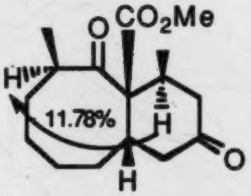
Fig. 8 The NOE results of compound **54**



For the Diels-Alder reaction of diene **46** and enone **35** (Entry 6), the ethereal solution of **35** and tin(IV) chloride was first stirred for 1 h at -78°C and then diene **46** was added. Two products **56** and **57** were obtained. TLC analysis indicated that the silyl group was eliminated during the reaction leading to dione **57**, mp 106-107°C, which was isolated in 98% yield along with a trace amount of **56**. In this reaction, the diene added to the dienophile exclusively from the proton face and *endo* to the ester group to give adduct **57** as the only stereoisomer. The high resolution mass spectrum of **57** displayed the molecular ion peak at m/z 280.16707 corresponding to the molecular formula $C_{16}H_{24}O_4$. In the ^{13}C NMR (APT) spectrum, three peaks at δ 214.5, 206.6, and 171.8 were due to the carbonyl groups. In the ^{1}H NMR spectrum, the signal at δ 3.42 was assigned to the methyl group of the ester moiety. The ring junction proton was shown at δ 2.73. Four methylene protons adjacent to the cyclohexanone carbonyl appeared at δ 2.40 (d, J = 14 Hz), 2.27 (dd, J = 5.5, 14 Hz), 2.18 (ddd, J = 2, 4.5 14 Hz), and 1.90 (ddd, J = 2.5, 2.5, 14

Hz), respectively. The other proton α to a ketone was observed at δ 2.47 as a multiplet. Two methyl doublets were also displayed, one at δ 1.02 (J = 6.5 Hz) and the other at δ 0.90 (J = 6.5 Hz). In the infrared spectrum, characteristic carbonyl absorptions were shown at 1733 (ester) and 1695 cm^{-1} (ketone). The depicted stereochemistry of the adduct **57**, as suggested by the NOE experiments (Fig. 9), was verified by an X-ray crystallographic analysis (Fig. 10).

Figure 9 The NOE result of compound **57**



In the high resolution mass spectrum of compound **56**, the molecular ion peak was found at m/z 436.30074 which was consistent with the molecular formula $C_{25}H_{44}O_4Si$. Two carbonyl bands were shown at 1694 (ketone) and 1739 cm^{-1} (ester) in the infrared spectrum along with a carbon-carbon double bond absorption at 1674 cm^{-1}. In the ^1H NMR spectrum, a doublet of doublets (J = 1, 6 Hz) at δ 4.92 was assigned to the vinyl proton. The methyl protons of the ester moiety was shown at δ 3.50 as a sharp singlet. The ring junction proton appeared as a broad triplet (J = 6 Hz) at δ 3.20. The two multiplets at δ 2.47 and 2.20 were assigned to the allylic protons at C-11. In the ^{13}C NMR (APT) spectrum, two carbonyl signals appeared at δ 215.9 (ketone) and 171.7 (ester). The two vinyl carbons were shown at δ 149.2 and 109.1, respectively. The stereochemistry of **56** was determined again using the NOE technique (Fig. 11).

Fig. 10 The three dimensional X-ray crystallographical structure of compound **57**

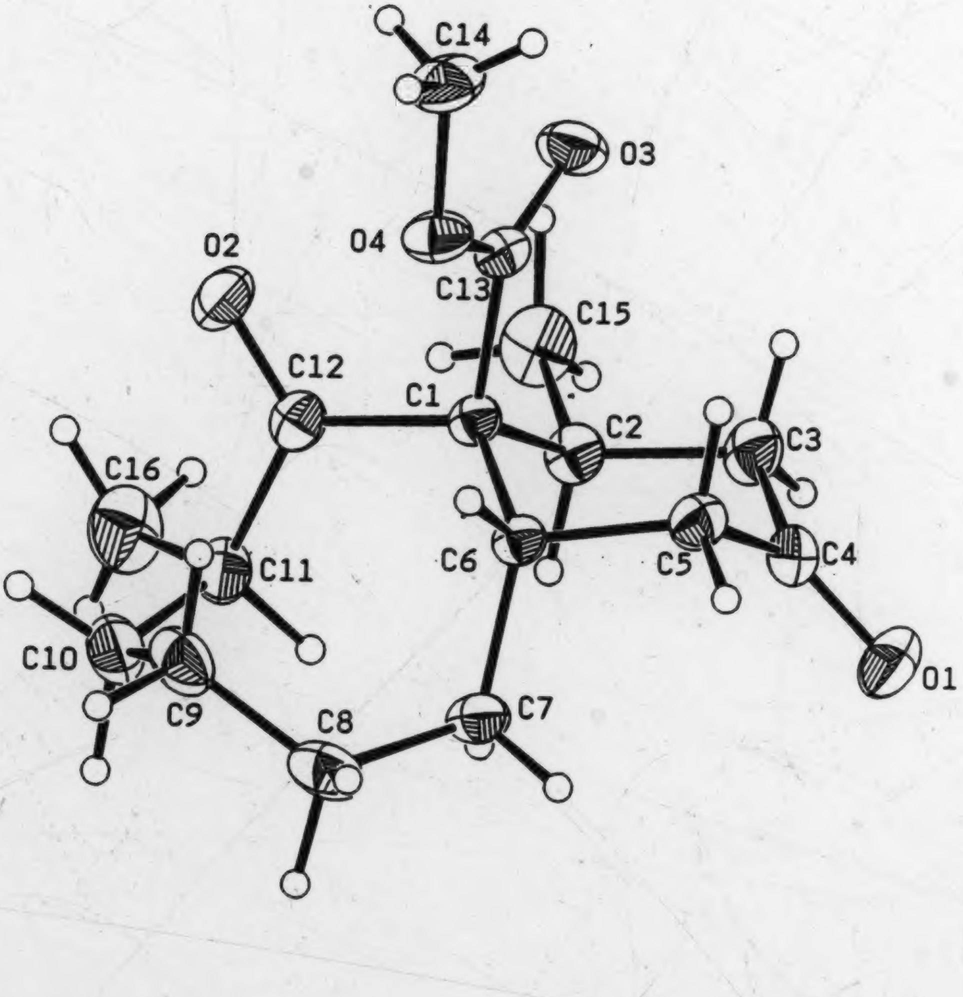
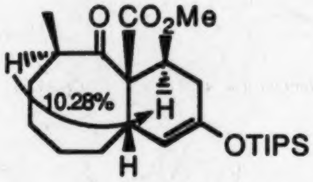
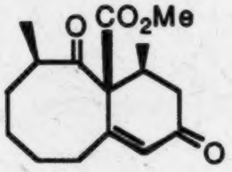


Figure 11 The NOE result of compound **56**



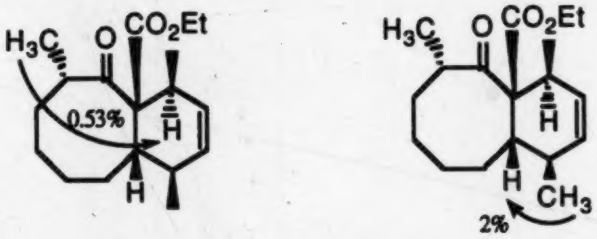
The regiochemistry of **56** was deduced by extensive proton spin decoupling experiments and confirmed by an oxidation reaction. Upon treatment with palladium acetate and benzoquinone in acetonitrile, compound **56** was oxidized to unsaturated ketone **67**. In the ^{1}H NMR spectrum, the vinylic proton was found at δ 4.75 as a doublet with coupling constant of 6 Hz. Two methyl doublets appeared at δ 1.12 (J = 7 Hz) and 1.05 (J = 7 Hz). The methyl group of the ester moiety was displayed at δ 3.60 as a sharp singlet. In the ^{13}C NMR (APT) spectrum, three carbonyls were displayed at δ 217.7 (ketone), 215.6 (ketone) and 172.11 (ester), while the two olefinic carbons were shown at δ 148.7 and 108.8.



67

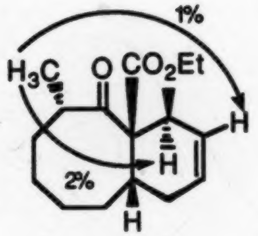
The Diels-Alder reaction of enone **36** and *trans*, *trans*-2,4-hexadiene (Entry 7) catalyzed by ferric chloride at -78°C gave adduct **58** in 92% yield. The reaction was completely stereoselective with exclusive addition of the diene from the methyl face of the dienophile via an *endo*-to-ester transition state. In the infrared spectrum, adduct **58** displayed two carbonyl bands at 1741 (ester) and 1714 cm^{-1} (ketone) and an olefinic double bond absorption at 1684 cm^{-1}. The molecular ion peak at m/z 292.20308 in the high resolution mass spectrum supported the required molecular formula of $C_{18}H_{28}O_3$. In the ^{13}C NMR APT spectrum, two carbonyl carbons and two olefinic carbons were displayed at δ 214.0 (ketone), 172.7 (ester), 131.5 (olefin) and 128.1 (olefin). In the ^{1}H NMR spectrum, two doublets of doublets of doublets at δ 5.56 (J = 3, 4, 10 Hz) and 5.21 (J = 1, 2, 10 Hz) were assigned to the vinylic protons and a pair of complex signals at δ 3.25 and 2.30 were assigned to the allylic protons.. The presence of the ester group was evident from the multiplet at δ 4.15 and the triplet (J = 7 Hz) at δ 1.22. Three methyl doublets with coupling constant of 7 Hz each were found at δ 1.08 (C-12 methyl), 0.95 (C-9 methyl) and 1.15 (C-3 methyl). The stereochemistry of the adduct **58** was determined by the NOE experiments. Results are diagrammatically shown in Figure 12.

Figure 12 The NOE results of compound **58**



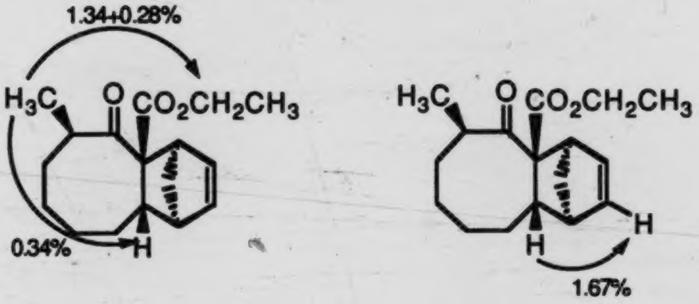
In the Diels-Alder reaction of *trans*-1,3-pentadiene and enone **36** (Entry 8), an inseparable mixture of **59** and **60** was obtained in a ratio of 4 : 1. The diene was added to the enone **36** from the methyl face via an *endo*-to-ester transition state to give the major adduct **59**. The minor isomer **60** was assumed to be a diastereomer produced following the *ortho*-rule, since no violation of the basic rules has been observed in any of the previous cases. The infrared spectrum of the mixture showed carbonyl bands at 1735 (ester) and 1695 cm^{-1} (ketone). In the high resolution mass spectrum, the molecular ion peak at m/z 278.39497 indicated the molecular composition of $C_{17}H_{26}O_3$. In the ^1H NMR spectrum, for the major isomer **59**, a pair of complex signals at δ 5.70 (ddd, J = 3.5, 7, 10 Hz) and 5.46 (ddd, J = 2, 4.5, 10 Hz) were assigned to the two vinyl protons. Both the proton at ring junction and the α-methine proton of the ketone appeared at δ 2.60 as a multiplet. The methylene protons of the ester moiety were shown at δ 4.24 as a multiplet, while the adjacent methyl group was observed at δ 1.25 as a triplet (J = 7 Hz). The methyl group at C-12 was shown at δ 0.98 as a doublet (J = 7.5 Hz) and the neighboring allylic proton was displayed at δ 2.87 as a multiplet. The other two allylic protons at C-9 were shown at δ 2.30 and 2.15. The α-methyl group of the ketone appeared at δ 1.08 as a doublet (J = 7 Hz). Again the stereochemistry was assigned with the aid of the NOE technique. Results are summarized in Fig 13. The stereochemistry of the minor product **60** remains to be confirmed.

Figure 13 The NOE results of compound **59**



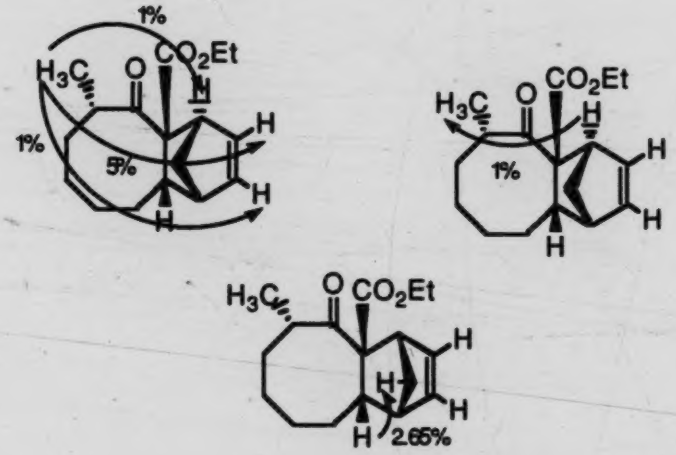
The Diels-Alder reaction of enone **36** and cyclopentadiene (Entry 9), gave two diastereomers **61** and **62**. The ratio of these two isomers varied with different Lewis acids. The reaction catalyzed by ferric chloride at -78°C gave the ratio of 2 : 1 in favor of **61**, while the reaction catalyzed by zinc chloride at room temperature gave the ratio of 1 : 1. The adduct **61** was formed as a result of addition of cyclopentadiene from the proton face of enone **36** and *endo* to the ester. On the other hand, the formation of adduct **62** involved approach of the diene from the methyl face of **36** and *endo* to its ketone carbonyl. The infrared spectrum of **61** showed two carbonyl bands at 1735 (ester) and 1689 cm^{-1} (ketone). The absorption at 3064 cm^{-1} indicated the presence of carbon-carbon double bond. The high resolution mass spectrum displayed the molecular ion peak at m/z 276.17267 which was consistent with the molecular formula $C_{17}H_{24}O_3$. In the ^{13}C NMR (APT) spectrum, carbonyl signals and olefinic carbon signals were shown at δ 213.3 (ketone), 172.2 (ester), 141.1 (olefin), and 135.5 (olefin), respectively. In the ^1H NMR spectrum, the doublets of doublets at δ 6.35 (J = 3, 5.5 Hz) and δ 5.93 (J = 3, 5.5 Hz) were assigned to the vinylic protons. The bridgehead protons appeared at δ 2.50 (m) and 2.00 (dddd, J = 1, 11, 11, 15 Hz). The ring junction proton was shown at δ 3.30 as a broad singlet. The methylene protons of ester moiety were observed at δ 3.98 and 4.15 as two doublets of doublets with coupling constants of 7.5 and 11 Hz each, while the adjacent methyl group was shown at δ 1.24 as a triplet (J = 7.5 Hz). A doublet at δ 1.10 (J = 7 Hz) was due to the α-methyl group of the ketone. In the NOE experiment, irradiation of the broad singlet at δ 3.30 (the ring junction proton) resulted in 1.67% enhancement on the vinylic proton at δ 6.35 (Fig. 14), indicating the depicted stereochemistry of the adduct **61**.

Figure 14 The NOE results of compound **61**



In the infrared spectrum of the adduct **62**, the vinylic C-H band was shown at 3010 cm^{-1} and the two carbonyl absorptions were displayed at 1736 (ester) and 1690 cm^{-1} (ketone). The molecular ion peak at m/z 276.17242 was shown in the high resolution mass spectrum, in agreement with the molecular formula of $C_{17}H_{24}O_3$. In its ^{13}C NMR APT spectrum, the carbonyl signals were found at δ 215.6 (ketone) and 174.0 (ester), and the two olefinic carbon signals appeared at δ 137.7 and 135.3. In the ^1H NMR spectrum, the vinylic protons were displayed at δ 6.32 (dd, J = 3, 5.5 Hz) and δ 6.25 (ddd, J =0.5, 3, 5.5 Hz). The two bridgehead protons were shown at δ 3.37 and δ 2.80 as a broad singlet and a multiplet, respectively. The methylene protons of the ester appeared at δ 4.20 as a multiplet and its adjacent methyl group was shown at δ 1.25 as a triplet (J = 7 Hz). The methine and methyl protons adjacent to the ketone were displayed at δ 2.80 (m) and 1.00 (d, J = 7 Hz), respectively. The doublet of doublets of doublets at δ 2.90 (J = 3, 3, 12 Hz) was assigned to the ring junction proton. The stereochemistry of the adduct was again determined with the aid of the NOE experiments. The NOE results are shown in Figure 15.

Figure 15 The NOE results of compound **62**



As shown above, the Lewis acid catalyzed Diels-Alder reaction of 2-carbalkoxy-8-methyl-2-cyclooctenones **35** and **36** occurred readily with a high degree of regio- and stereoselectivity. All reactions carried out in this investigation follow the empirical *ortho-* and *para*-rule very well and are quite predictable. The stereoselectivity favoring *endo*-to-ester adducts is exhibited due to sterically disfavored *endo*-to-ketone transition state. Both the conformation of the eight-membered cyclic dienophiles **35** and **36** and the substitution pattern of the diene counterpart seem to play a very important role in the high facial selectivity generally observed for the reaction. Thus, it is possible to control the stereoselectivity by suitable choice of substituent(s) of the diene. This study presents an efficient and very straightforward synthetic method for the construction of bicyclo[6.4.0]dodecane ring skeleton.

Experimental

General

Melting point were recorded on a Kofler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet 7199 or Nicolet MX-1 FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker WH-200, Bruker WH-300, Bruker WH-400, or UNITY-500 using deuterochloroform ($CDCl_3$) as solvent unless otherwise stated. The chemical shift of the deuterated solvent peak (for $CDCl_3$: δ = 7.25 ppm, for C_6D_6: δ = 7.15 ppm) was used as an internal reference. Coupling constants are reported to ± 0.5 Hz. Chemical shift measurements are reported in ppm units downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH-300 (75 MHz) NMR spectrometer as solutions in deuterochloroform ($CDCl_3$) as the internal standard setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test). Methyl and methine groups are shown as singlets antiphase (a) with respect to the deuterochloroform signal, whereas methylene groups, quaternary carbons and carbonyl groups appear in phase (p) with it. Nuclear Overhauser enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon for 10 minutes prior to use. Two dimensional (2D) homonuclear correlation spectrum (COSY) and proton spin decoupling experiments were performed on the Bruker WH-300 MHz NMR machine using the standard proton parameters. High resolution electron impact mass spectra (HRMS) were recorded using an A.E.I. model MS-50 mass spectrometer. Chemical ionization mass spectra (CIMS) were recorded on an A.E.I. MS-12 mass spectrometer, using ammonia as the reagent gas. Spectral data are reported as m/z values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. X-ray analyses were performed by Professor Yu Wang and coworkers at National Taiwan University. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 20% ethyl acetate in Skelly B means 20 parts of ethyl acetate by volume to 80 parts of Skelly B by volume.

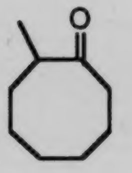
Materials

Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. All reactions were carried out under a positive pressure of argon. Solvents were distilled under argon from appropriate drying agents before use. Tetrahydrofuran (THF), diethyl ether, toluene and 1,2-dimethoxyethane (DME) were freshly distilled from a blue or purple solution of sodium benzophenone ketyl.

Diisopropylamine was distilled from sodium hydroxide or potassium hydroxide. Pyridine, benzene, dichloromethane and triethylamine (TEA) were distilled from calcium hydride. Reactions requiring anhydrous conditions were performed using oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. Argon was passed through a column of 4 Å molecular sieves, with a self-indicating silica gel (coarse grained) as the indicator. Flash chromatography developed by Still was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography. Skellysolve B (Skelly B) refers to Skelly Oil Company light petroleum, bp 62 - 70°C. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck, Darmstadt). Ultraviolet active materials were detected by visualization under a UV lamp (254 or 350 nm). For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, w/v) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate.

I. The preparation of dienophiles

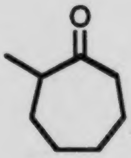
2-Methylcyclooctanone (37)[35]



Diisopropylamine (2.62 mL, 0.02 mol, 2 eq) was dissolved in 12.5 mL of dry THF and cooled to 0°C with an ice-water bath with stirring under argon atmosphere. A solution of *n*-butyllithium (1.6 M in THF, 12.5 mL, 2 eq) was then added dropwise over a 20 min period followed by cooling to -78°C. A solution of cyclooctanone (1.26 g, 0.01 mol, 1 eq) in 5 mL of dry THF was added dropwise over 30 min. The solution was stirred at -78°C for 30 min followed by rapid addition of methyl iodide (1.24 mL, 0.02 mol, 2 eq). After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 40 h. The reaction mixture was quenched with 25 mL of water and the aqueous layer was extracted with ether three times (10 mL each). The organic layers were combined, washed twice with water (10 mL each) and once with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product , a yellow oil (1.8 g), was subjected to flash chromatography on silica gel, eluting with 2.5% ethyl acetate in Skelly B, to give 2-methylcyclooctanone (**37**) (0.86 g, 89% yield based on the consumed starting material) along with a 30% recovery of the starting material.

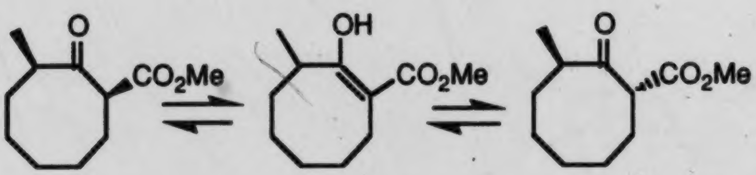
IR ($CHCl_3$ cast): 1701 (C=O), 1376 cm^{-1} (CH_3); ^1H NMR (300 MHz in $CDCl_3$) δ: 2.55 (m, 1H, $CHCH_3$), 2.35 (m, 2H, $CH_2C{=}O$), 1.00 (d, 3H, $J = 7$ Hz, CH_3); ^{13}C NMR (APT 75 MHz in $CDCl_3$) δ: 220.3 (p), 45.3 (a), 40.4 (p), 33.2 (p), 26.4 (p), 26.0 (p), 25.2 (p), 24.1 (p), 6.9 (a); HRMS m/z (M^+) calcd. for $C_9H_{16}O$: 140.12012; found: 140.11977.

2-Methylcycloheptenone (39)



This compound was prepared in 80% yield from cycloheptanone by Dr. J.B. Kim using a procedure similar to that described above.

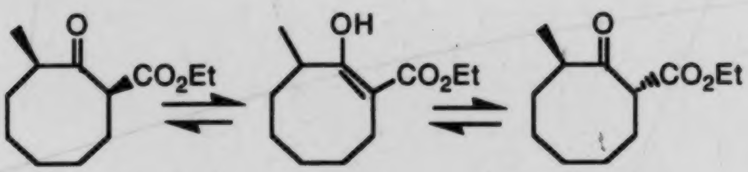
2-Carbomethoxy-8-methylcyclooctanone (38)



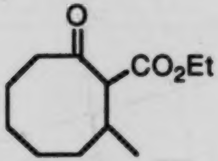
To a suspension of sodium hydride (8.57 g, 0.214 mol, 60% in oil) in 60 mL of dry DME was added pre-dried dimethyl carbonate (32.17 g, 0.357 mol) . The mixture was heated to reflux with stirring under argon atmosphere. A solution of 2-methylcyclooctanone (37) (10 g, 0.714 mol) in 20 mL of DME was added dropwise and the reaction mixture refluxed for 19 h, then cooled to the 0°C with an ice-water bath. A 10% aqueous solution of acetic acid was added with stirring until the solution became acidic. The mixture was then separated and the aqueous layer was extracted with ether three times (30 mL each). The organic layers were combined, washed with water (30 mL), saturated aqueous solution of sodium bicarbonate (30 mL), water (30 mL) and saturated aqueous solution of sodium chloride (30 mL), dried over magnesium sulfate, filtered and then concentrated. Flash chromatography of the residue on silica gel, eluting with 2.5% ethyl acetate in Skelly B, gave the ß-keto ester **38** (12.0 g, 85% yield) as a colorless oil. This compound was shown by the following spectral data to exist as a mixture of two keto forms (2 : 1, total 68%) and an enol form (32%).

IR ($CHCl_3$, cast) 1749 (C=O, ester), 1707 (C=O, ketone), 1640 (C=O, ester, enol form), 1609 (C=C, enol form), 1365 cm^{-1} (CH_3); ^1H NMR (300 MHz in $CDCl_3$) δ: 13.47 (d, 0.33H, J = 1.5 Hz, OH, enol form), 3.46 (dd, 0.22H, J = 5, 10.5 Hz, $OCCHCO_2Me$, minor keto form), 3.29 (dd, 0.45H, J = 3, 15.5 Hz, $OCCHCO_2Me$, major keto form), 3.36 (s, 1.35H, OCH_3, ester, major keto form), 3.31 (s, 0.66H, OCH_3, ester, minor keto form), 3.25 (s, 0.99H, OCH_3, ester, enol form), 1.55 (d, 1.35H, J = 7 Hz, CH_3, major keto form), 1.06 (d, 0.99H, J = 7 Hz, CH_3, enol form), 1.01 (d, 0.66H, J = 7 Hz, CH_3, minor keto form); ^{13}C NMR (75 MHz in $CDCl_3$) for the major keto form δ: 213.1 (p), 178.5 (p), 56.2 (a), 51.1 (a), 45.2 (a), 37.9 (p), 31.3 (p), 28.2 (p), 26.1 (p), 24.5 (p), 19.1 (a); The following minor ^{13}C NMR signals were observed for the other two isomers: 212.4 (p), 173.8 (p), 170.5 (p), 170.3 (p), 99.6 (p), 54.9 (a), 51.6 (a), 51.5 (a), 46.3 (p), 34.8 (p), 34.4 (a), 31.4 (p), 30.1 (p), 27.4 (p), 26.2 (p), 25.6 (p), 25.0 (p), 24.4 (p), 17.0 (a),13.9 (a); HRMS m/z (M^+) calcd. for $C_{11}H_{18}O_3$: 198.12560; found: 198.12635. Anal. calcd. for $C_{11}H_{18}O_3$: C 66.64%, H 9.15%; found: C 66.90%, H 9.15%.

2-Carbethoxy-8-methylcyclooctanone (40) and 2-carbethoxy-3-methylcyclooctanone (41)



40



41

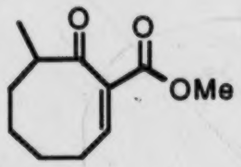
To a solution of 2-methylcycloheptanone (**39**) (2.56 g, 0.02 mol) in 50 mL of dry ether cooled to 0°C under an argon atmosphere was added boron trifluoride etherate (3.94 mL, 0.032 mol). A solution of ethyl diazoacetate (3.31 mL, 0.032 mol) in 5 mL of dry ether was then added dropwise over a 10 min period followed by warming to room temperature. After 24 h, the reaction mixture was cooled to 0°C and a saturated aqueous solution of sodium bicarbonate was added to the mixture until pH 7. The aqueous layer was extracted three times with ether (10 mL each) and the organic layers were combined, washed twice with water (10 mL each), and once with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was subjected to flash chromatography on silica gel. Elution with 5% ethyl acetate in Skelly B gave first 2-carbethoxy-8-methylcyclooctanone (**40**) (2.4 g, 56%) and then 2-carbethoxy-3-methylcyclooctanone (**41**) (1.6 g, 38%).

Compound **40** was shown by the following spectral data to exist as a mixture of two keto forms (4 : 1, total 78%) and an enol form (22%). IR ($CHCl_3$ cast): 1747 (C=O, ester), 1708 (C=O, ketone), 1638 (C=O, ester in enol form), 1610 cm^{-1} (C=C in enol form); ^{1}H NMR (300 MHz in $CDCl_3$) δ: 12.89 (d, 0.22H, OH in enol form), 4.19 (q, 0.44H, J = 7 Hz, OCH_2, enol form), 4.15 - 4.05 (m, 1.56H, OCH_2, two keto forms), 3.85 (dd, 0.2H, J = 4, 11 Hz, $COCHCO_2Et$, minor keto form), 3.50 (dd, 0.58H, J = 3.5, 12 Hz, $COCHCO_2Et$, major keto form), 1.95 (t, 0.66H, J = 7 Hz, OCH_2CH_3, minor keto form), 1.28 (t, 0.66H, J = 7 Hz, OCH_2CH_3, enol form), 1.21 (t, 1.74H, J = 7 Hz, OCH_2CH_3, major keto forms), 1.12 (d, 0.66H, J = 7 Hz, CH_3, enol form), 1.11 (d, 1.74H, J = 7Hz, CH_3, major keto forms), 0.95 (d, 0.66H, J = 7 Hz, CH_3, minor keto form); ^{13}C NMR (75 MHz in $CDCl_3$) for the major keto form δ: 215.0 (p), 170.24 (p) 61.1 (p), 56.4 (a), 45.1 (a), 35.0 (p), 28.5 (p), 25.9 (p), 25.6 (p), 24.2 (p), 19.0 (a), 14.0 (a); The following minor ^{13}C NMR signals were observed for the other two isomers: 213.7 (p), 177.9 (p), 170.15 (p), 99.6 (p), 60.9 (p), 60.1 (p), 55.0 (a), 46.4 (a), 37.7 (p), 34.1 (a), 31.3 (p), 30.9 (p), 30.2 (p), 27.2 (p), 26.0 (p), 24.7 (p), 24.5 (p), 24.4 (p),16.7 (a), 14.3 (a), 13.7 (a); HRMS m/z (M^+) calcd. for $C_{12}H_{20}O_3$: 212.14125; found 212.14087.

Compound **41** was shown by the following spectral data to exist completely in the keto form: IR ($CHCl_3$, cast): 1745 (C=O, ester), 1705 (C=O, ketone), 1385 cm^{-1} (CH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.10 (m, 2H, OCH_2), 3.30 (d, 1H, J = 11 Hz, $COCHCO_2Et$), 2.75 - 2.56 (m, 1H, CHHC=O), 2.54 - 2.23 (m, 1H, CHHC=O), 1.20 (t, 3H, J = 7 Hz, OCH_2CH_3), 0.95 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 211.0 (p), 169.4 (p), 64.7 (a), 61.1 (p), 42.0 (p), 34.7 (a), 34.5

(p), 27.3 (p), 25.6 (p), 23.6 (p), 20.7 (a), 14.1 (a); HRMS m/z (M^+) calcd. for $C_{12}H_{20}O_3$: 212.14125; found 212.14058.

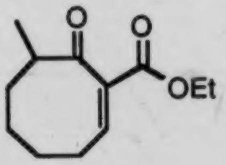
2-Carbomethoxy-8-methyl-2-cyclooctenone (35)



Sodium hydride (1.02 g, 60% in oil, 25.3 mmol, 5 eq) was suspended in 10 mL of dry THF with stirring under argon atmosphere and cooled to 0°C. A solution of 2-carbomethoxy-8-methylcyclooctanone (**38**) (1.0 g, 5.05 mmol, 1 eq) in 5 mL of dry THF was added dropwise to the suspension over a 15 min period. When the formation of the sodium enolate was complete and the hydrogen gas evolution ceased, a thick suspension developed. Stirring and cooling were continued for 20 min. Then a solution of phenylselenenyl chloride (4.86 g, 25.3 mmol, 5 eq) in 10 mL of dry THF was added. The reaction mixture was stirred at 0°C for another 15 min, then poured into a solution of ether and aqueous saturated sodium bicarbonate. The aqueous layer was extracted three times with ether (10 mL each). All the organic layers were combined, washed with water twice (10 mL each) and saturated aqueous sodium chloride solution once (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was dissolved in 20 mL of dichloromethane. The solution was stirred at 0°C and aqueous H_2O_2 (30%, 2 mL) was added dropwise to the solution. When oxidation was complete, as indicated by the discharge of the yellow color of the solution, the ice-water bath was removed. The reaction mixture was warmed to room temperature with vigorous stirring for 20 min and then cooled again to 0°C. After 15 min, the suspension of benzeneselenenic acid was filtered off. The filtrate was washed once with 10 mL of saturated aqueous solution of sodium bicarbonate, twice with water (10 mL each) and once with saturated aqueous solution of sodium chloride (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was subjected to flash chromatography on silica gel. Elution with 10% ethyl acetate in Skelly B gave 2-carbomethoxy-8-methyl-2-cyclooctenone (**35**) (0.86 g, 86%) as a colorless oil. This compound was shown by the following spectral data to exist exclusively in the keto form.

IR ($CHCl_3$ cast): 1723 (C=O, ester), 1695 (C=O, ketone), 1640 (C=C), 1379 (α-CH_3), 1365 cm^{-1} (OCH_3); ^1H NMR (300 MHz in $CDCl_3$) δ: 7.18 (t, 1H, J = 4.5 Hz, =CH), 3.68 (s, 3H, OCH_3), 2.60 (m, 1H, $CHCH_3$), 2.34 (m, 2H, =$CHCH_2$), 1.10 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz in $CDCl_3$) δ: 211.0 (p), 165.0 (p), 147.0 (a), 131.4 (p), 52.2 (a), 47.5 (a), 30.2 (p), 29.7 (p), 26.0 (p), 21.5 (p), 15.33 (a); HRMS m/z (M^+) calcd. for $C_{11}H_{16}O_3$: 196.10984; found: 196.11022. Anal. calcd. for $C_{11}H_{16}O_3$: C 67.32%, H 8.22%; found: C 67.23%, H 8.31%.

2-Carbethoxy-8-methyl-2-cyclooctenone (36)



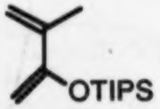
This compound was prepared from keto ester **40** in 85% yield using the phenylselenenylation-oxidative elimination process detailed above. The compound **36** also existed exclusively in the keto form as shown by the following spectral data: IR ($CHCl_3$ cast): 1720 (C=O. ester), 1696 (C=O, ketone), 1639 (C=C), 1378 (CH_3), 1369 cm^{-1} (CH_3, ester); ^{1}H NMR (300 MHz in $CDCl_3$) δ: 7.18 (t, 1H, J = 4.5 Hz, =CH), 4.27 (m, 2H, OCH_2), 2.60 (m, 1H, $CHCH_3$), 2.35 (dd, 2H, J = 4.5, 10 Hz, CH_2CH=), 1.23 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.14 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz in $CDCl_3$) δ: 211.0 (p), 164.6 (p), 146.0 (a), 131.9 (p), 61.1 (p), 47.7 (a), 30.2 (p), 29.9 (p), 26.1 (p), 21.6 (p), 15.6 (a), 14.1 (a); HRMS m/z (M^+) calcd. for $C_{12}H_{18}O_3$: 210.12560; found 21.12554. Anal. calcd. for $C_{12}H_{18}O_3$: C 68.55%, H 8.63%; found C 68.45%, H 8.50%.

II. The preparation of trialkylsilyloxy substituted 1,3-butadienes

General procedure

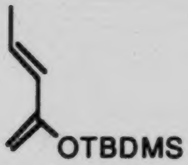
Diisopropylamine (0.25 mL, 1.8 mmol, 1.5 eq) was dissolved in 5 mL of dry THF and cooled to 0°C with an ice-water bath with stirring under argon atmosphere. A solution of *n*-butyllithium (1.6 M in THF, 1.2 mL, 1.90 mL, 1.5 eq) was added dropwise over a 20 min period. The resulting LDA was then cooled to -78°C followed by dropwise addition of a solution of the corresponding substituted methyl vinyl ketone (100 mg, 1.2 mmol, 1 eq) in 5 mL of dry THF over a period of 30 min. The solution was stirred at -78°C for 30 min followed by rapid addition of the corresponding trialkylsilyl chloride (1.8 mmol, 1.5 eq). The reaction mixture was allowed to warm to room temperature after 15 min and stirred at room temperature for 40 h. The reaction mixture was quenched with 10 mL of water and the aqueous layer was extracted with Skelly B three times (10 mL each). The organic solutions were combined, washed twice with water (10 mL each) and once with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product , a yellow oil, was purified by bulb-to-bulb distillation to give the product.

2-Triisopropylsilyloxy-3-methyl-1,3-butadiene (44)



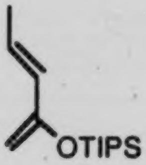
This compound was prepared from 3-methyl-3-buten-2-one using triisopropylsilyl chloride as a trapping reagent. Bulb-to-bulb distillation of the crude product at 80°C / 0.2 mmHg gave the desired diene **44** in a yield of 70%. The structure was characterized by the following spectral data. IR (hexane cast): 1590 (C=C-O), 1384 (CH_3), 1023, 819 cm^{-1} (Si-O-C); ^1H NMR (300 MHz in C_6D_6) δ: 5.70 (ddd, 1H, J = 0.5, 0.5, 2.5 Hz, CHH=C(CH_3)), 5.00 (s, br, CHH=C(CH_3)), 4.45 (s, 1H, CHH=C(OTIPS)), 4.35 (s, 1H, CHH=C(OTIPS)), 1.75 (s, 3H, CH_3C=), 1.13 - 1.11 (m, 21H, CH, CH_3 on TIPS); ^{13}C NMR (75 MHz in C_6D_6) δ: 157.2 (p), 140.2 (p), 113.9 (p), 91.7 (p), 19.9 (a), 18.3 (a), 13.2 (a); HRMS m/z (M^+) calcd. for $C_{14}H_{28}OSi$: 240.19095; found: 240.18995.

trans-2-*tert*-Butyldimethylsilyloxy-1,3-pentadiene (45)



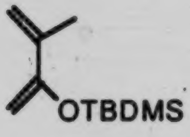
Diene **45** was prepared from 3-penten-2-one using *tert*-butyldimethylsilyl chloride as a trapping reagent. Bulb-to-bulb distillation of the crude product and collecting the fraction at 70°C / 0.5 mmHg gave the diene in 85% yield. The structure of **45** was deducted from the following spectral data. IR (neat film): 1657 and 1641 (C=C, conjugated), 1593 (C=C-O), 1023, 826 cm^{-1} (Si-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ: 6.17 (qd, 1H, J = 7, 14 Hz, $CH_3CH=CH$), 5.88 (qd, 1H, J = 2, 14 Hz, $CH_3CH=CH$), 4.29 (s, 1H, =CHH), 4.22 (s, 1H, =CHH), 1.58 (dd, 3H, J = 2, 7 Hz, $CH_3CH=$), 0.99 (s, br, 9H, 3 $(CH_3)_3C$), 0.15 (s, br, 6H, 2 CH_3); ^{13}C NMR (APT, 75 MHz, C_6D_6) δ: 155.4 (p), 129.8 (a), 126.0 (a), 93.4 (p), 25.8 (a), 18.3 (p), 17.3 (a), -4.7 (a); HRMS m/z (M^+) calcd. for $C_{14}H_{28}OSi$: 240.19095; found: 240.18995.

trans-2-Triisopropylsilyloxy-1,3-pentadiene (46)



This compound was prepared from 3-penten-2-one using triisopropylsilyl chloride as a trapping reagent. The crude product was purified by bulb-to-bulb distillation. Diene **46** (90% yield) was collected at 40°C / 0.5 mmHg in 90% yield. The structure was confirmed by the following spectral data. ^{1}H NMR (300 MHz, C_6D_6) δ: 6.25 (qd, 1H, J = 7, 14 Hz, CH_3CH=CH), 5.88 (qd, 1H, J = 2, 14 Hz, CH_3CH=CH), 4.29 (s, br, 1H, HHC=), 4.19 (s, br, 1H, HHC=), 1.60 (ddd, 3H, J = 2, 7 Hz, =$CHCH_3$), 1.13 (m, 3H, $SiCH(CH_3)_2$), 1.02 (d, 18H, J = 6.5 Hz, 3 $CH(CH_3)_2$); ^{13}C NMR (300 MHz, C_6D_6) δ: 155.8 (p), 130.0 (a), 126.1 (a), 92.8 (p), 18.3 (a), 17.9 (a), 12.64 (a); HRMS m/z (M^+) cacld. for $C_{14}H_{28}OSi$: 240.19095; found 240.18994.

2-*tert*-Butyldimethylsilyloxy-3-methyl-1,3-butadiene (43)



This compound was prepared in 92% yield from 3-methyl-3-buten-2-one using *tert*-butyldimethylsilyl chloride as a trapping reagent by Miss Judy Yip of our laboratory using the same procedure described above.

III. Diels-Alder Reactions

General procedure for $FeCl_3$ catalyzed Diels-Alder reactions

To an ethereal solution (3 mL) of enones **35** or **36** (0.24 mmol, 1 eq) was added the diene (2.4 mmol, 10 eq). Lewis acid (1 eq) was then added and the resulting solution stirred under an argon atmosphere. The progress of the reaction was monitored by TLC. Upon completion, a saturated aqueous sodium bicarbonate solution was added. The ether layer was separated and the aqueous layer was extracted three times with ether (10 mL each). The combined ether solutions were washed with water (10 mL), and saturated aqueous sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate-Skelly B) to give the desired adduct(s). Yield, time, and temperature of each reaction are shown in Tables 3 and 4 in the Results and Discussion section. When more than one product was obtained, products are presented in order of isolation from flash chromatography.

General procedure for $SnCl_4$ and $BF_3 \cdot OEt_2$ catalyzed Diels-Alder reactions

Basically, the $SnCl_4$ and $BF_3 \cdot OEt_2$ catalyzed Diels-Alder reactions were carried out using the same general procedure as that described above for the $FeCl_3$ catalyzed Diels-Alder reactions. Yields and reaction conditions are shown in Tables 3 and 4 in the Results and Discussion section.

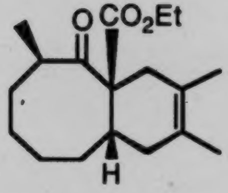
The procedure for $ZnCl_2$ catalyzed Diels-Alder reactions

Zinc chloride (2 eq) was fused in a reaction flask under an argon atmosphere and dissolved in dry ether (3 mL). A solution of enone **36** (50 mg, 0.24 mmol, 1 eq) in dry ether (1 mL) was added. After stirring at room temperature under an argon atmosphere for 30 minutes, diene (2.4 mmol, 10 eq) was then added. The resulting mixture was stirred at room temperature under an argon atmosphere. The reaction was monitored with TLC and upon completion, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The ether layer was separated and the aqueous layer was extracted three times with ether (10 mL each). The combined ether solutions were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate-Skelly B) to give the desired adduct(s). Yields and reaction conditions are shown in Tables 3 and 4 in the Results and Discussion section.

The procedure for the tin(IV) chloride catalyzed Diels-Alder reaction of trialkylsilyloxy substituted dienes 44, 45, and 46.

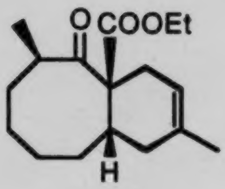
Tin(IV) chloride (1 eq) was added to an ethereal solution (3 mL) of enone **35** (0.24 mmol, 1 eq) cooled to -78°C and stirred for a certain period of time to allow for the formation of the complex of tin(IV) chloride and the dienophile **35**. Then an ethereal solution (1 mL) of diene (0.48 mmol, 2 eq) was added and the reaction was monitored by TLC. Upon completion of the reaction, saturated aqueous sodium bicarbonate solution was added. The ether layer was separated and the aqueous layer was extracted three times with ether (10 mL each). The combined ether solutions were washed with water (10 mL), saturated aqueous sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified by flash chromatography to give the desired product(s). Yields of products and individual reaction conditions are compiled in Table 4.

(1S*, 3R*, 8S*)-1-Carbethoxy-3,10,11-trimethylbicyclo[6.4.0]-dodec-10-en-2-one (47)



IR (CHCl$_3$, cast): 1737 (C=O ester), 1695 (C=O ketone), 1374 cm^{-1} (CH$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.15 (m, 2H, OCH$_2$), 3.25 (m, 1H, CH$_3$CHC=O), 2.66 (m, 2H, =CCH$_2$, C-9), 2.59 (s, 2H, CH$_2$C=, C-12), 1.63 (s, br, 3H, =CCH$_3$), 1.54 (s, br, 3H, =CCH$_3$), 1.21 (t, 3H, J = 7 Hz, OCH$_2$CH$_3$), 1.04 (d, 3H, J = 7 Hz, CHCH$_3$); ^{13}C NMR (APT, 75 MHz, CDCl$_3$) δ: 216.8 (p), 172.2 (p), 124.0 (p), 121.7 (p), 64.4 (a), 60.9 (p), 42.1 (a), 40.0 (p), 36.5 (p), 32.4 (p), 31.9 (p), 26.5 (p), 25.5 (p), 25.8 (p), 19.4 (p), 19.0 (p), 15.3 (a), 14.1 (a); HRMS m/z (M$^+$) calcd.: for C$_{18}$H$_{28}$O$_3$: 292.20386; found 292.20349. Anal. cacld. for C$_{18}$H$_{28}$O$_3$: C 73.93%, H 9.65%; found C 74.02%, H 9.42%.

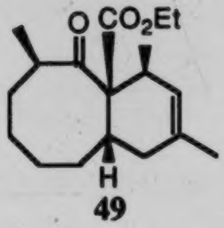
(1S*, 3R*, 8S*)-1-Carbethoxy-3,10-dimethylbicyclo[6.4.0]-dodec-10-en-2-one (48)



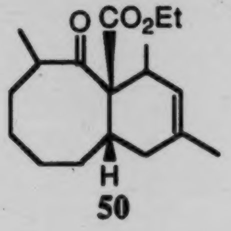
IR (CHCl$_3$, cast): 1695 (C=O, ketone), 1737 cm^{-1} (C=O ester); ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.33 (m, 1H, =CH), 4.17 (m, 2H, OCH$_2$), 3.25

(m, 1H, $CHCH_3$), 2.82 - 2.50 (m, 4H, $CH_2CH{=}C(CH_3)CH_2$), 1.60 (s, 3H, $CH_3C{=}$), 1.23 (t, 3H, OCH_2CH_3), 1.04 (d, 3H, J = 6.5 Hz, CH_3); ^{13}C NMR (APT, 75 MHz in $CDCl_3$) δ: 216.9 (p), 172.2 (p), 132.4 (p), 116.9 (a), 63.3 (p), 61.0 (p), 42.1 (a), 38.4 (p), 36.6 (p), 36.5 (a), 32.4 (p), 26.4 (p), 26.3 (p), 25.9 (p), 23.6 (a), 19.3 (a), 14.0 (a); HRMS m/z (M^+) calcd. for $C_{17}H_{26}O_3$: 278.18820; found 278.18771. Anal. calcd. for $C_{17}H_{26}O_3$: C 73.35%, H 9.41%; found C 73.35%, H 9.59%; INPET: irr. H at δ 5.33 (4946 Hz), found C signals from ^{13}C NMR at δ 63.3 (C ring juction), 38.4 ($=CHCH_2$), 26.3 ($=C(CH_3)CH_2$), 23.7 ($=CCH_3$); irr. H at δ 3.25 (4337.4 Hz), found C signals from ^{13}C NMR at δ 217.0 (C=O ketone), 36.6 ($CH_2CH(CH_3)$), 25.9(CH_2), 19.3 ($CHCH_3$); irr. H at δ 1.04 (3679.3 Hz) found C signals from ^{13}C NMR at δ 217.0 (C=O ketone), 42.1 ($CH(CH_3)$).

(1R*, 3R*, 8S*, 12S*)-1-Carbethoxy-3,10,12-trimethylbicyclo-[6.4.0]dodec-10-en-2-one (49) and diastereomer 50



49



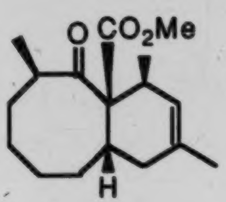
50

In this Diels-Alder reaction, an inseparable mixture of **49** and **50** was obtained in a ratio of 4 : 1. For the mixture: IR ($CHCl_3$, cast): 1723 (C=O, ester), 1696 cm^{-1} (C=O, ketone); HRMS m/z (M^+) calcd. for $C_{18}H_{28}O_3$: 292.20386; found 292.20374. Anal. calcd. for $C_{18}H_{28}O_3$: C 73.93%, H 9.65%, found C 73.90%, H 9.69%.

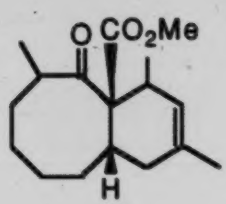
For the major isomer **49**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.08 (m, 1H, =CH), 4.15 (m, 2H, OCH_2), 2.85 (m, 1H, $(CH_3)CHCH=$), 2.60 (m, 1H, CH, ring junction), 2.55 (m, 1H, CHC=O), 2.29 (dd, 1H, J = 6, 18 Hz, CHHC=), 2.05 (dd, 1H, J = 6, 18 Hz, CHHC=), 1.60 (s, 3H, $=CCH_3$), 1.20 (t, 3H, J = 7 Hz, OCH_2CH_3), 0.95 (d, 3H, J = 6.5 Hz, $CH(CH_3)C=O$), 0.88 (d, 3H, J = 7.5 Hz, $CH(CH_3)CH=$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.3 (p), 173.5 (p), 132.2 (p), 125.0 (a), 65.3 (p), 60.9 (p), 45.2 (a), 38.8 (a), 38.4 (a), 34.7 (p), 33.5 (p), 31.2 (p), 26.0 (p), 23.3 (a), 21.0 (p), 18.9 (a), 17.9 (a), 14.1 (a).

For the minor isomer **50**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18 (s, br, =CH), 1.26 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.19 (d, 3H, J = 7 Hz, CH_3), 1.12 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ 171.9 (p), 131.4 (p), 124.3 (a), 65.8 (p), 60.4 (P), 41.8 (a), 38.6 (p), 37.0 (a), 36.1 (p), 31.6 (a), 31.2 (p), 26.2 (p), 25.0 (p), 23.3 (a), 20.0 (a), 18.9 (a), 16.1 (a).

(1R*, 3R*, 8S*, 12S*)-1-Carbomethoxy-3,10,12-trimethylbicyclo[6.4.0]dodec-10-en-2-one (51) and diastereomer 52



51



52

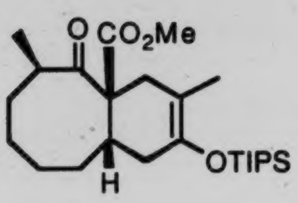
For the mixture of **51** and **52**: IR ($CHCl_3$, cast): 1733 (C=O, ester), 1699 cm^{-1} (C=O, ketone); HRMS m/z (M^+) calcd. for $C_{17}H_{26}O_3$:

278.18820; found 278.18799. Anal. calcd. for $C_{17}H_{26}O_3$: C 73.35%, H 9.42%, found C 73.46%; H 9.35%.

For the major isomer **51**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.13 (m, 1H, =CH), 3.72 (s, 3H, OCH_3), 2.84 (m, 1H, (CH_3)CHCH=), 2.60 (m, 1H, CH, ring junction), 2.50 (m, 1H, CHC=O), 2.30 (dd, 1H, J = 10.5, 19 Hz, CHHC=), 2.07 (dd, 1H, J = 8, 19 Hz, CHHC=), 1.67 (s, 3H, =CCH_3), 0.98 (d, 3H, J = 6.5 Hz, CH(CH_3)C=O), 0.90 (d, 3H, J = 7.0 Hz, CH(CH_3)CH=); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.2 (p), 174.1 (p), 132.2 (p), 125.0 (a), 65.4 (p), 51.9 (a), 45.2 (a), 38.8 (a), 38.46 (a), 34.7 (p), 33.5 (p), 31.0 (p), 26.0 (p), 22.8 (a), 21.1 (p), 18.8 (a), 17.9 (a).

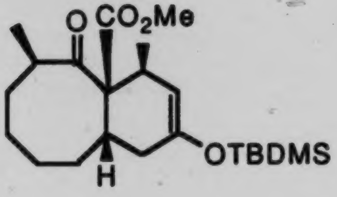
For the minor isomer **52**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18 (s, br, =CH), 3.67 (s, 3H, OCH_3), 3.13 (m, 1H, $CHCH_3$), 2.97 (m, 1H, CHC=O), 1.15 (d, 3H, J = 7.5 Hz, CH_3C=O), 1.09 (d, 3H, J = 7.5 Hz, CH_3CHCH=); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 131.3 (p), 124.3 (a), 66.8 (p), 51.5 (a), 41.9 (a), 38.54 (p), 36.6 (a), 36.0 (p), 31.7 (a), 26.1 (p), 24.7 (p), 23.4 (a), 19.9 (a), 18.0 (a).

(1S*, 3R*, 8S*)-1-Carbomethoxy-10-triisopropylsilyloxy-3,11-dimethylbicyclo[6.4.0]dodec-10-en-2-one (53)

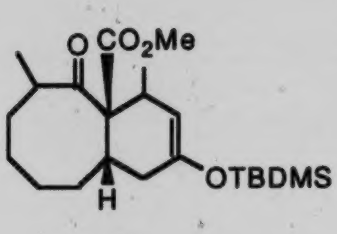


In this reaction, the solution of dienophile **35** and tin(IV) chloride was stirred for 20 min at -78°C and then the diene **44** was added dropwise. The adduct **53** was obtained as the only isomer in 90% yield. IR ($CHCl_3$, cast): 1744 (C=O, ester), 1696 (C=O, ketone), 1658 cm^{-1} (C=C); ^1H NMR (300 MHz, C_6D_6) δ: 3.40 (s, 3H, OCH_3), 3.05 (d, br, 1H, J = 18 Hz, CHHC(OTIPS)=), 2.95 - 2.85 (m, 2H, $CHCH_3$ and CH ring junction), 2.83 (d, 1H, J = 18 Hz, $CHHC(CH_3)$=), 2.64 (d, br, 1H, J = 18 Hz, $CHHC(CH_3)$=), 1.77 (s, 3H, =CCH_3), 1.73 (d, 1H, J = 18 Hz, CHHC(OTIPS)=), 1.25 -1.00 (m, 26H, 3 $SiCH(CH_3)_2$, 2 CH_2 and CHH), 0.97 (d, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, C_6D_6): δ: 215.1 (p), 172.1 (p). 142.2 (p), 106.8 (p), 63.8 (p), 51.9 (a), 42.0 (a), 39.0 (p), 37.9 (a), 36.5 (p), 32.6 (p), 31.3 (p), 26.3 (p), 26.1 (p), 19.5 (a), 18.3 (a, 3C), 16.6 (a), 13.5 (a, 6C); HRMS m/z (M^+) calcd. for $C_{25}H_{44}O_4Si$: 436.30090; found 436.30084. Anal. cacld. for $C_{25}H_{44}O_4Si$: C 68.76%, H 10.16%; found C 68.87%, H 10.30%.

(1R*, 3R*, 8S*, 12S*)-10-*tert*-Butyldimethylsilyloxy-1-carbomethoxy-3,12-dimethylbicyclo[6.4.0.]dodec-10-en-2-one (54) and diastereomer 55



54



55

In this reaction, the solution of enone **35** and tin(IV) chloride was stirred for 20 min at -78°C and then diene **45** was added. The mixture of

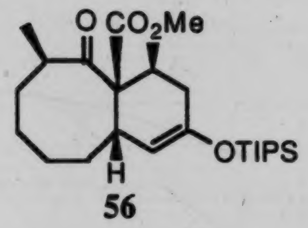
54 and **55** was obtained in 89% yield as an inseparable mixture of two isomers in the ratio of 2 : 1. The structure was established by the following spectral data. The regiochemistry of compound **54** was deduced with the aid of spin decoupling experiments.

For the mixture: IR ($CHCl_3$, cast): 1730 (C=O, ester), 1694 (C=O, ketone); HRMS (M^+) m/z cacld. for $C_{22}H_{30}O_4Si$: 394.25294; found 394.25318.

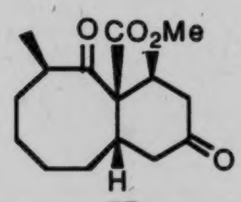
For the major isomer **54**: ^1H NMR (300 MHz, C_6D_6) δ: 4.72 (s, br, 1H, =CH), 3.32 (s, 3H, OCH_3), 3.15 (m, 1H, CH_3CHCH=), 2.93 (m, 1H, CH_3CHC=O), 2.30 (dddd, 1H, J = 1.5, 3, 9.5, 18 Hz, C**H**H, C-9), 2.10 (dddd, 1H, J = 1.5, 3, 7.5, 18 Hz, CH**H**, C-9), 1.27 (d, 3H, J = 7 Hz, CH_3CHC=O), 1.17 (d, 3H, J = 7.5 Hz, CH_3CHCH=), 1.00 (s, 9H, $SiC(CH_3)_3$), 0.19 (m, 6H, 2 $SiCH_3$); ^{13}C NMR (APT, 75 MHz, C_6D_6) δ: 211.8 (p), 173.4 (p), 148.6 (p), 107.7 (a), 65.4 (p), 51.4 (a), 46.9 (a), 41.4 (a), 39.0 (p), 38,8 (a), 33.6 (p), 31.4 (p), 26.7 (p), 26.5 (a), 25.9 (a, 3C), 21.3 (p), 19.8 (a), 18.8 (a), 18.2 (p), 14.3 (a).

For the minor isomer **55**: ^1H NMR (300 MHz, C_6D_6) δ: 4.78 (s, br, 1H, =CH), 3.39 (s, 3H, OCH_3), 2.83 (M, 1H, CH_3CHCH=), 2.55 (m, 1H, CH_3CHC=O), 1.15 (d, 3H, J = 7.5 Hz, CH_3CHC=O), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 6H, 2 $SiCH_3$); ^{13}C NMR (APT, 75 MHz, C_6D_6) δ: 215.3 (p), 171.8 (p), 108.2 (a), 67.0 (p), 51.2 (a), 36.5 (p), 37.8 (a), 33.7 (p), 32.3 (p), 31.2 (p), 30.9 (a), 26.0 (a, 3C), 24.9 (p), 22.8 (p), 19.9 (a), 18.9 (a), 14.6 (a), 11.6 (a).

(1R*, 3R*, 8S*, 12S*)-1-Carbomethoxy-10-triisopropylsilyloxy-3,12-dimethylbicyclo[6.4.0]dodec-9-en-2-one (56) and (1R*, 3R*, 8S*, 12S*)-1-Carbomethoxy-3,12-dimethylbicyclo-[6.4.0]dodecane-2,10-dione (57)



56



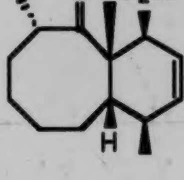
57

To an ethereal solution (10 mL) of enone **35** (448 mg, 2.3 mmol) cooled to -78°C was added $SnCl_4$ (597 mg, 0.27 mL, 2.29 mmol). After stirring for 1 h at -78°C under an argon atmosphere, the diene **46** (1.1 g, 4.58 mmol) was added to the reaction mixture via syringe and the reaction was monitored with TLC. Upon completion of the reaction, saturated sodium bicarbonate solution was added. The ether layer was separated and the aqueous layer was extracted three times with ether (10 mL each). The combined ether solutions were washed with water (10 mL) and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. Flash chromatography of the residue gave dione **57** in 98% yield (630 mg). A trace amount (10 mg, 1% yield) of the faster-moving adduct **56** was also obtained. These two compounds were identified as follows.

Compound **56**: IR ($CHCl_3$, cast): 1739 (C=O, ester), 1694 (C=O, ketone), 1674 cm^{-1} (C=C); ^{1}H NMR (300 MHz, C_6D_6) δ: 4.92 (dd, 1H, J = 1, 6 Hz, =CH), 3.50 (s, 3H, OCH_3), 3.20 (t, br, 1H, J = 6 Hz, CH, ring junction), 2.70 (m, 1H, $CH(CH_3)C=O$), 2.47 (dd, br, 1H, J = 10, 16 Hz, CHHCOTIPS), 2.20 (m, 2H, CHHCOTIPS, $CHCH_3$), 1.22 (d, 3H, J = 6.5 Hz, $CHCH_3$), 1.02 (d, 3H, J = 6 Hz, CH_3CHCO), 1.11 (s, 18H, 3 $SiCH(CH_3)_2$, 1.08 (s, 3H, 3 $SiCH(CH_3)_2$); ^{13}C NMR (APT, 75 MHz, C_6D_6) δ: 215.9 (p), 171.7 (p), 149.2 (p), 109.1 (a), 68.4 (p), 51.3 (a), 40.5 (a), 38.9 (a), 37.8 (p), 37.0 (p), 31.2 (p), 29.3 (a), 28.2 (p), 23.6 (p), 20.2 (a), 18.2 (a, 6C), 18.1 (a), 13.0 (a, 3C); HRMS: M^+ (m/z) calcd. for $C_{25}H_{44}O_4Si$: 436.30090; found 436.30074.

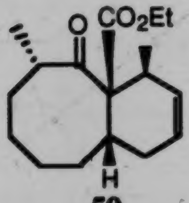
Compound **57**, mp 106 - 107°C (hexane): IR ($CHCl_3$, cast): 1733 (C=O, ester), 1695 cm^{-1} (C=O, ketone); ^1H NMR (300 MHz, C_6D_6) δ: 3.42 (s, 3H, OCH_3), 2.73 (m, 1H, $CH_3CHC=O$), 2.40 (dd, 1H, J = 14, 14 Hz, CHHC=O), 2.27 (dd, 1H, J = 5.5, 14 Hz, CHHC=O), 2.18 (ddd, 1H, J = 2, 4.5, 14 Hz, CHHC=O), 2.09 (ddd, 1H, J = 4.5, 6.5, 13 Hz, $CHCH_3$). 1.90 (td, 1H, J = 2.5, 14 Hz, CHHC=O), 1.02 (d, 3H, J = 6.5 Hz, CH_3), 0.90 (d, 3H, J = 6.5 Hz, CH_3CH, C-12); ^{13}C NMR (APT, 75 MHz, C_6D_6) δ: 214.5 (p), 206.6 (p), 171.8 (p), 68.9 (p), 51.5 (a), 48.6 (p), 46.7 (p), 40.7 (a), 39.9 (a), 37.0 (p), 33.3 (a), 28.5 (p), 27.1 (p), 23.1 (p), 19.9 (a), 18.4(a); HRMS m/z (M^+) calcd. for $C_{16}H_{24}O_3$: 280.16745; found 280.16707. Anal. calcd. for $C_{16}H_{24}O_3$: C 68.55%, H 8.63%; found C 68.72%, H 8.89%.

(1R*, 3S*, 8S*, 9R*, 12S*)-1-Carbethoxy-3,9,12-trimethylbicyclo[6.4.0]dodec-10-en-2-one (58)

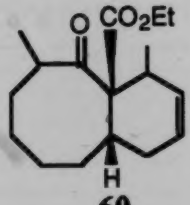


IR ($CHCl_3$, cast): 3012 (=CH), 1741 (C=O ester), 1714 (C=O ketone), 1684 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ: 5.56 (ddd, 1H, J = 3, 4, 10 Hz, =CH), 5.21 (ddd, 1H, J = 1, 2, 10 Hz, =CH), 4.15 (m, 2H, OCH_2), 3.25 (m, 1H, CHCH=), 3.15 (dt, 1H, J = 5, 10 Hz, CH, ring junction), 2.81 (qdd, 1H, J = 3, 7, 11 Hz, CH_3CHCO), 2.30 (m, 2H, CHCH= and CHH on C-7), 1.4 - 1.9 (m, 7H, $3CH_2$ and CHH on C-7), 1.22 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.15 (d, 3H, CH_3CHCO, J = 7 Hz), 1.08 (d, 3H, J = 7 Hz, $CH_3CHCH=$), 0.95 (d, 3H, J = 7 Hz, $CH_3CHCH=$); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 214.0 (p), 172.7 (p), 131.5 (a), 128.1 (a), 69.4 (p), 61.5 (p), 49.5 (a), 39.9 (a), 33.39 (a), 32.8 (p), 32.5 (p), 27.0 (p), 25.9 (p), 24.9 (p); HRMS m/z (M^+) calcd. for $C_{18}H_{28}O_3$: 292.20386; found 292.20308. Anal. calcd. for $C_{18}H_{28}O_3$: C 73.93%, H 9.65%; found C 73.87%, H 9.64%.

(1R*, 3S*, 8S*, 12S*)-1-Carbethoxy-3,12-dimethylbicyclo-[6.4.0]dodec-10-en-2-one (59) and diastereomer 60



59



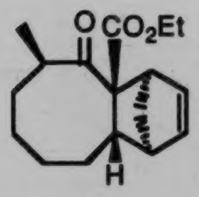
60

Compound **59** and its diastereomer **60** were obtained as an inseparable mixture in a ratio of 4 : 1. For the mixture: IR ($CHCl_3$, cast): 3425 (=C-H), 3022 (=C-H), 1735 (C=O, ester), 1695 cm^{-1} (C=O, ketone); HRMS m/z (M^+) calcd. for $C_{17}H_{26}O_3$: 278.39497, found 278.39497. Anal. calcd. for $C_{17}H_{26}O_3$: C 73.35%, H 9.41%, found C 73.38%, H 9.40%.

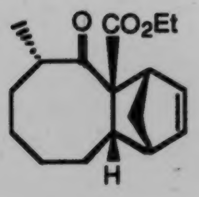
For the major isomer **59**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.70 (ddd, 1H, J = 3.5, 7, 10 Hz, CH=), 5.46 (ddd, 1H, J = 2, 4.5, 10 Hz, CH=), 4.24 (m, 2H, OCH_2), 2.87 (m, 1H, CH_3CHCH=), 2.6 (m, 2H, CH, ring junction, and CH_3CHCO), 2.30, (m, 1H, CHHCH=), 2.15 (m, 1H, CHHCH=), 1.25 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.08 (d, 3H, J = 7.5 Hz, CH_3CHC=O), 0.98 (d, 3H, J = 7.5 Hz, CH_3CHCH=); ^{13}C NMR (75 MHz, $CDCl_3$): δ: 213.9 (p), 173.3 (p), 130.6 (a), 124.8 (a), 65.2 (p), 61.0 (p), 45.9 (a), 38.2 (a), 38.0 (a), 34.1 (p), 30.1 (p), 28.8 (p), 26.3 (p), 21.0 (p), 19.4 (a), 17.2 (a), 14.1 (a).

For the minor isomer **60**: ^{1}H NMR (500 MHz in $CDCl_3$) δ: 5.58 (m, 1H, =CH), 5.49 (ddd, 1H, J = 2, 4.5, 10 Hz, =CH), 4.18 (m, 2H, OCH_2), 2.54 (m, 1H, CHHCH=), 1.28 (t, 3H, J = 7.5 Hz, OCH_2CH_3), 1.22 (d, 3H, J = 7.5 Hz, CH_3), 1.14 (d, 3H, J = 6.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.9 (p), 171.8 (p), 130.2 (a), 124.1 (a), 65.2 (p), 60.5 (p), 41.9 (a), 40.4 (a), 36.2 (a), 33.6 (p), 31.1 (p), 29.7 (p), 26.0 (p), 24.8 (p), 20.0 (a), 18.0 (a), 14.1 (a).

(1R*, 2R*, 4R*, 9S*, 10S*)-2-Carbethoxy-4-methyltricyclo-[8.2.1.0^{2,9}]tridec-11-en-3-one (61) and (1S*, 2R*, 4S*, 9S*, 10R*)-2-Carbethoxy-4-methyltricyclo[8.2.1.0^{2,9}]tridec-11-en-3-one (62)



61

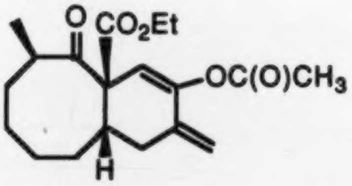


62

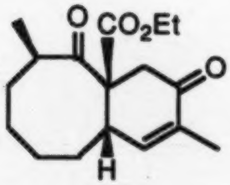
For compound **61**: IR ($CHCl_3$, cast): 3064 (=C-H), 1735 (C=O, ester), 1689 cm^{-1} (C=O, ketone); ^{1}H NMR (300 MHz, $CDCl_3$): δ: 6.35 (dd, 1H, J = 3, 5.5 Hz, =CH, C-11), 5.93 (dd, 1H, J = 3, 5.5 Hz, =CH, C-12), 4.15 (qd, 1H, J = 7.5, 11 Hz, OCHH), 3.98 (qd, 1H, J = 7.5, 11 Hz, OCHH), 3.30 (s, 1H, CH, ring junction), 2.49 - 2.60 (m, 3H, =CHCH, $CHCH_3$, CHCHH), 2.00 (dddd, 1H, J = 1, 11, 11, 15 Hz, CHCH=), 1.24 (t, 3H, J = 7.5 Hz, OCH_2CH_3), 1.10 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ: 213.3 (p), 172.2 (p), 141.1 (a), 135.5 (a), 60.8 (p), 68.7 (p), 54.1 (a), 53.8 (a), 51.8 (a) 49.1 (a), 47.0 (p), 33.4 (p), 31.4 (p), 31.2 (p), 29.7 (p), 21.9 (a), 13.9 (a); HRMS m/z (M^+) calcd. for $C_{17}H_{24}O_3$: 276.17255, found: 276.17267. Anal. calcd. for $C_{17}H_{24}O_3$: C 73.88%, H 8.75%; found C 73.69%, H 8.92%.

For compound **62**: IR ($CHCl_3$, cast): 3010 (=C-H), 1736 (C=O, ester), 1690 cm^{-1} (C=O, ketone); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.32 (dd, 1H, J = 3, 5.5 Hz, =CH, C-11), 6.25 (ddd, 1H, J = 0.5., 3, 5.5 Hz, =CH, C-12), 4.20 (m, 2H, OCH_2), 3.37 (s, 1H, CHCH=), 2.90 (ddd, 1H, J = 3, 3, 12 Hz, CH, ring junction), 2.80 (m, 2H, CHCH= and $CHCH_3$), 1.25 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.00 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 215.6 (p), 174.0 (p), 137.7 (a), 135.3 (a), 71.3 (p), 61.3 (p), 54.5 (a), 49.9 (a), 49.2 (a), 49.1 (p), 45.8 (a), 33.9 (p), 31.3 (p), 28.3 (p), 25.4 (p), 19.7 (a), 14.0 (a); HRMS m/z (M^+) calcd. for $C_{17}H_{24}O_3$: 276.17255; found 276.17242. Anal. calcd. for $C_{17}H_{24}O_3$: C 73.88%, H 8.75%; found C 74.20%, H 8.90%.

(1R*, 3R*, 8S*)-11-Acetoxy-1-carbethoxy-3-methyl-10-methylenebicyclo[6.4.0]dodec-11-en-2-one (63) and (1S*, 3R*, 8S*)-1-Carbethoxy-3,10-dimethylbicyclo[6.4.0]dodec-9-ene-2,11-dione (64)



63



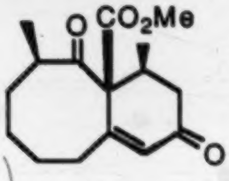
64

A gentle stream of oxygen was bubbled through a solution of the Diels-Alder adduct **48** (50 mg, 0.18 mmol), acetic anhydride (0.025 mL, 0.27 mmol), pyridine (0.021 mL, 0.27 mmol), 5,10,15,20-tetraphenyl-21*H*, 23*H*-porphine (5 mg) and 4-dimethylaminopyridine (catalytic amount) in 40 mL of carbon tetrachloride for 20 min. The bubbling was continued while the solution was irradiated with two 200W tungsten light bubbles for 35 h. After turning off the light, bubbling was continued for another 19 h. The solution was diluted with 20 mL of ether and then washed with saturated aqueous sodium bicarbonate (15 mL), aqueous 1 M HCl (15 mL) and saturated aqueous sodium chloride solution (10 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and concentrated to give the crude product. This crude product was subjected to flash chromatography. Elution with 5% ethyl acetate in Skelly-B gave first the compound **63** (16.3 mg, 31% yield) and then compound **64** (7 mg, 13% yield).

For compound **63**: IR (CH_2Cl_2, cast): 1767 (C=O, acetate), 1761 (C=O, ketone), 1744 (C=O, ester), 1682 (C=C, endocyclic), 1678 cm^{-1} (C=C, exo); ^1H NMR (300 MHz, $CDCl_3$) δ: 5.70 (s, 1H, =CH), 5.10 (m, 1H, =CHH), 4.95 (s, 1H, =CHH), 4.18 (m, 2H, OCH_2), 3.12 (m, 1H, $CHCH_3$), 2.80 (dddd, 1H, J = 2, 2, 4, 15 Hz, $CHHC{=}CH_2$), 2.70 (m, 1H, CH, ring junction), 2.30 (s, 3H, $COCH_3$), 2.20 (dd, 1H, J = 3, 15 Hz, $CHHC{=}CH_2$), 1.20 (t, 3H, J = 7 Hz, OCH_2CH_3), 0.90 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ: 215.5 (p), 199.0 (p), 170.4 (p), 147.0 (p), 134.7 (p), 114.0 (a), 111.6 (p), 65.5 (p), 61.5 (p), 42.2 (a), 41.3 (a), 38.1 (p), 34.4 (p), 29.5 (p), 28.7 (p), 24.9 (p), 20.8 (a), 19.1 (a); HRMS m/z (M^+) calcd. for $C_{19}H_{26}O_5$: 334.17801; found 334.17771.

For compound **64**: IR ($CHCl_3$, cast): 1738 cm^{-1} (C=O, ester), 1698 (C=O, ketone), 1682 (C=O, conj. ketone); ^1H NMR (300 MHz, $CDCl_3$) δ: 6.60 (dq, 1H, J = 1, 5.5 Hz, =CH), 4.15 (m, 2H, OCH_2), 3.40 (m, 1H, CHCH=), 3.15 (m, 1H, $CHCH_3$), 3.05 (s, br, 2H, CH_2CO), 1.72 (d, 3H, J = 1 Hz, $=CCH_3$), 1.19 (t, 3H, J = 7 Hz, OCH_2CH_3), 1.09 (d, 3H, J = 7 Hz, CH_3). ^{13}C NMR (APT 75 MHz, $CDCl_3$) δ: 213.0 (p), 195.2 (p), 171.1 (p), 148.1 (a), 133.3 (a), 64.5 (p), 61.9 (p), 42.2 (a), 41.6 (a), 38.3 (p), 35.5 (p), 27.9 (p), 26.5 (p), 26.1 (p), 19.5 (a), 15.5 (a), 14.0 (a); HRMS m/z (M^+) calcd. for $C_{17}H_{24}O_4$: 292.16745; found 292.16791.

(1R*, 3R*, 12S*)-1-Carbomethoxy-3,12-dimethylbicyclo[6.4.0]dodec-8-ene-2,10-dione (67)



At room temperature, to the well stirred acetonitrile solution (2 mL) of palladium(II) acetate (4.5 mg, 0.035 mmol) and benzoquinone (3.78 mg, 0.35 mmol) was added the acetonitrile solution (1 mL) of compound **56** (30 mg, 0.069 mmol). After stirred for 68 h, the reaction mixture was quenched by addition of water. This mixture was extracted with ether three time (5 mL each). The ethereal solutions were combined, washed with water (5 mL), aqueous saturated solution of sodium chloride (5 mL), and dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to the flash chromatography. Elution with 10% ethyl acetate in Skelly B gave the product **67** (23 mg) in 83% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (d, 1H, J = 6 Hz, =CH), 3.60 (s, 3H, OCH_3), 1.12 (d, 3H, J = 7 Hz, CH_3), 1.05(d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ 217.7 (p), 215.6 (p), 172.1(p), 148.7 (p), 108.8 (a), 68.4 (p), 51.6 (a), 40.9 (a), 38.6 (a), 37.8 (p), 36.6 (p), 31.0 (p), 29.2 (a), 28.0 (p), 23.4 (p), 20.0 (a).

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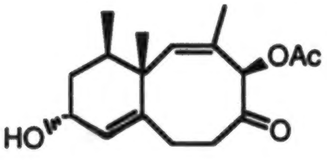
Chapter Two

Synthetic Studies on Neolemnane and Neolemnanyl Acetate

Introduction

Neolemnane (**68**) and its acetate **69** were first isolated from *L. africana* collected in Palau, Western Caroline Islands by Fenical and Clardy in 1981.[1] Because of their unusually terpenoid skeleton, the authors suggested the semisystematic name of neolemnane. The biological activity of these two natural products remains unclear and further investigation into this area is required.



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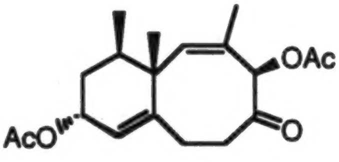


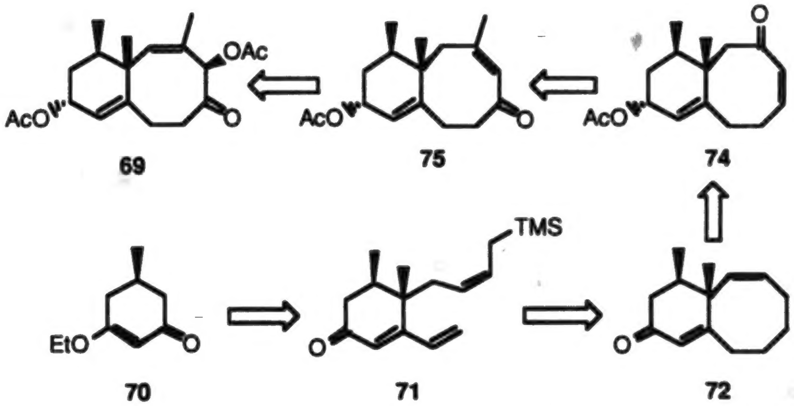
69

Neolemnane (**68**), a crystalline compound with mp 111-112°C, was obtained as the major terpenoidal compound (3% of the crude extract). The structure was deduced by the spectroscopic methods and the stereochemistry was established with the aid of X-ray crystallographic analysis. The low resolution mass spectrum showed the molecular ion peak at m/z 292 for $C_{17}H_{24}O_4$. In the infrared spectrum, the two carbonyl absorption bands were observed at 1739 and 1715 cm^{-1}, while the hydroxyl group displayed its absorption at 3600 cm^{-1}. In the ^{13}C NMR spectrum, the four oxygen-bearing carbons displayed their signals at δ 190.8 (s), 170.4 (s), 76.2 (d) and 63.5 (d), while the signals at δ 149.5, 138.7, 127.1 and 125.9 were assigned to the four vinyl carbons. The methyl group of the acetate moiety appeared at δ 20.5 as a quartet. With the information obtained from these spectroscopic analyses, the authors suggested that neolemnane (**68**) existed as a bicyclic hydroxy ketone of probable sesquiterpenoid origin. In the ^{1}H NMR spectrum, it was obvious that only three methyl groups attached to the bicyclic framework, a vinylic methyl at δ 1.68, a bridgehead methyl at δ 1.01, and a secondary methyl at δ 0.98 (d, J = 6.8 Hz), The hydroxyl group was recognized as allylic because the hydroxymethine proton at δ 4.14 was coupled (J = 4.9 Hz) to an vinylic proton at δ 5.86. The very low field singlet at δ 6.81 was assigned to the acetoxymethine proton which was considered to be at the α-position of the ketone.

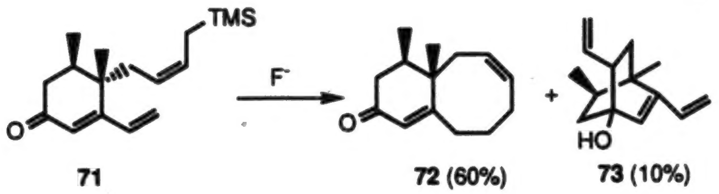
Neolemnanyl acetate (**69**), an oil which showed highly analogous ^{1}H NMR features when compared with **68**, was isolated as a minor component (0.15% of the extract). Acetylation of **68** produced a diacetate which was identical with the naturally occurring **69**. The acetate **69** exhibited the following spectral features: IR ($CHCl_3$): 1745, 1730, 1715 and 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.38 (s, 1H,), 5.87 (d, 1H, J = 5.0 Hz), 5.51 (s, 1H), 5.22 (s, 1H), 2.11 (s, 3H), 2.00 (s, 3H), 1.70 (s, 3H), 1.00 (s, 3H), 0.98 (d, 3H, J = 7.2 Hz); LRMS showed a molecular ion peak at m/z 334 corresponding to the molecular formula $C_{19}H_{26}O_5$.

Since their isolation, two total syntheses of **68** and **69** have been accomplished. One of them was reported along with the introduction of a new ring closure methodology in a full paper by Majetich and his co-workers.[2] The other constitutes a part of the Ph.D. dissertation by Ham of Ohio State University.[3] The retro-synthetic scheme of Majetich's synthesis is shown in Scheme 7. In this work, the construction of the fused bicyclo[6.4.0]dodecane skeleton was facilitated by the intramolecular Michael reaction of trienone **71** induced by the allylic carbanion generated

Scheme 7 Majetich's retro-synthesis of **68** and **69**

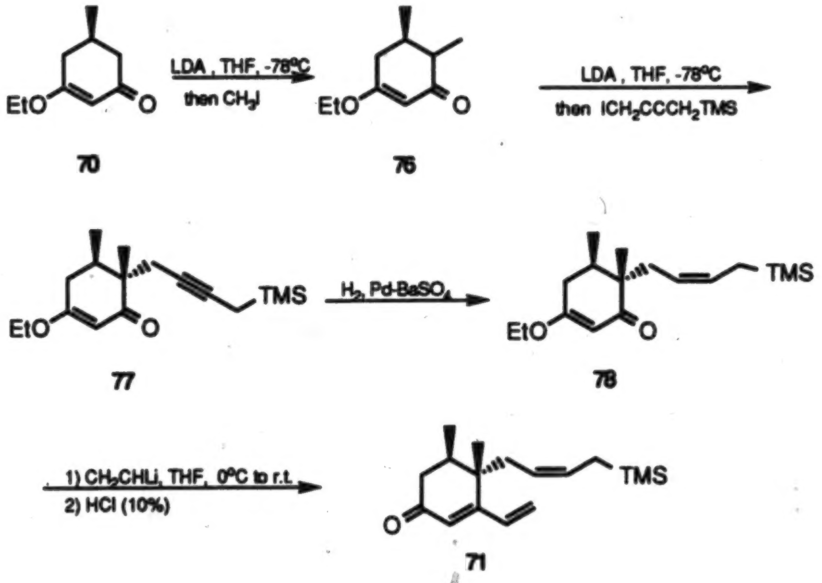


Scheme 8



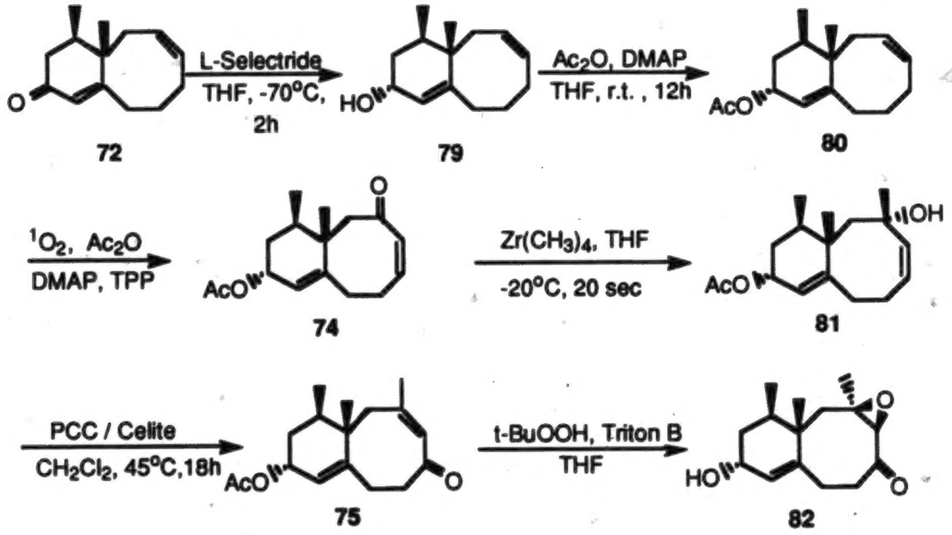
in situ from the corresponding allylsilane using fluoride ion (Scheme 8). Trienone **71** was prepared from **70** as shown in Scheme 9. The *cis*-C(13), C(15)-dimethyl relationship of neolemnane found in trienone **71** was achieved by successive alkylation, first with methyl iodide (**70** → **76**) then with 1-iodo-4-trimethylsilyl-2-butyne (**76** → **77**). Selective hydrogenation of compound **77** was achieved by the use of Lindlar catalyst. Dienone **78** thus obtained was converted to trienone **71** by sequential treatment with vinyllithium and aqueous hydrochloric acid. Cyclization of **71** using fluoride ion yielded the eight-six fused bicyclic enone **72** in 60% yield along with a small amount of tricyclic alcohol **73** (Scheme 8). The generation of the required axial allylic alcohol at C(10) from the cyclohexenone system was achieved by using L-selectride as a reducing reagent. The use of this bulky hydride reagent afforded a 1 : 4 mixture of alcohols (95% combined yield) favoring the desired epimer **79** (Scheme 10).

Scheme 9



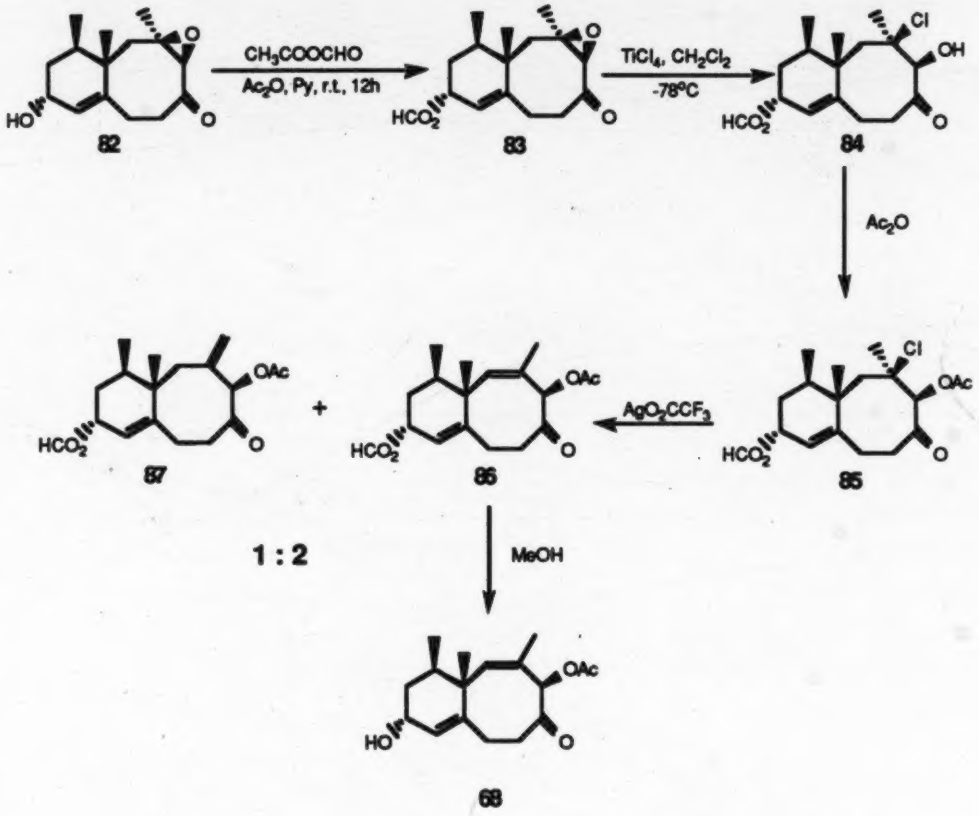
The modification of the cyclooctene ring of **80** began with the conversion of its olefinic double bond to an enone system using a photo-oxygenation reaction. Methylation of enone **74** at C(3) was effected using tetramethylzirconium to give the desired alcohol **81** in a 86% yield. Then enone **75** was prepared by oxidative rearrangement of alcohol **81** induced by PCC on celite. Epoxidation of enone **75** gave intermediate **82** which was used in the preparation of both neolemnane (**68**) and neolemnanyl acetate (**69**).

Scheme 10

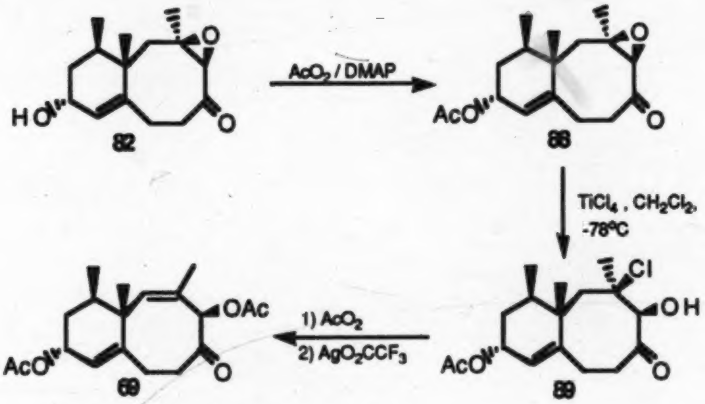


Two synthetic approaches, as outlined in Schemes 11 (for **68**) and 12 (for **69**) were developed in the final functionality transformations from compound **82** to the target molecules. Upon treatment with acetic formic anhydride, the hydroxyl group of **82** was protected in the form of formate ester **83**. The epoxide ring of **83** was then opened by treatment with a strong Lewis acid, titanium(IV) chloride to give chlorohydrin **84**. The acetylation product **85** was then treated with silver trifluoracetate to give compound **86** and **87**. Finally, the formyl protecting group of **86** was selectively removed by $KHCO_3$ in aqueous methanol to give neolemnane (**68**).

Scheme 11 The preparation of neolemnane (**68**) from compound **82**



Scheme 12 The preparation of compound **69** from **82**

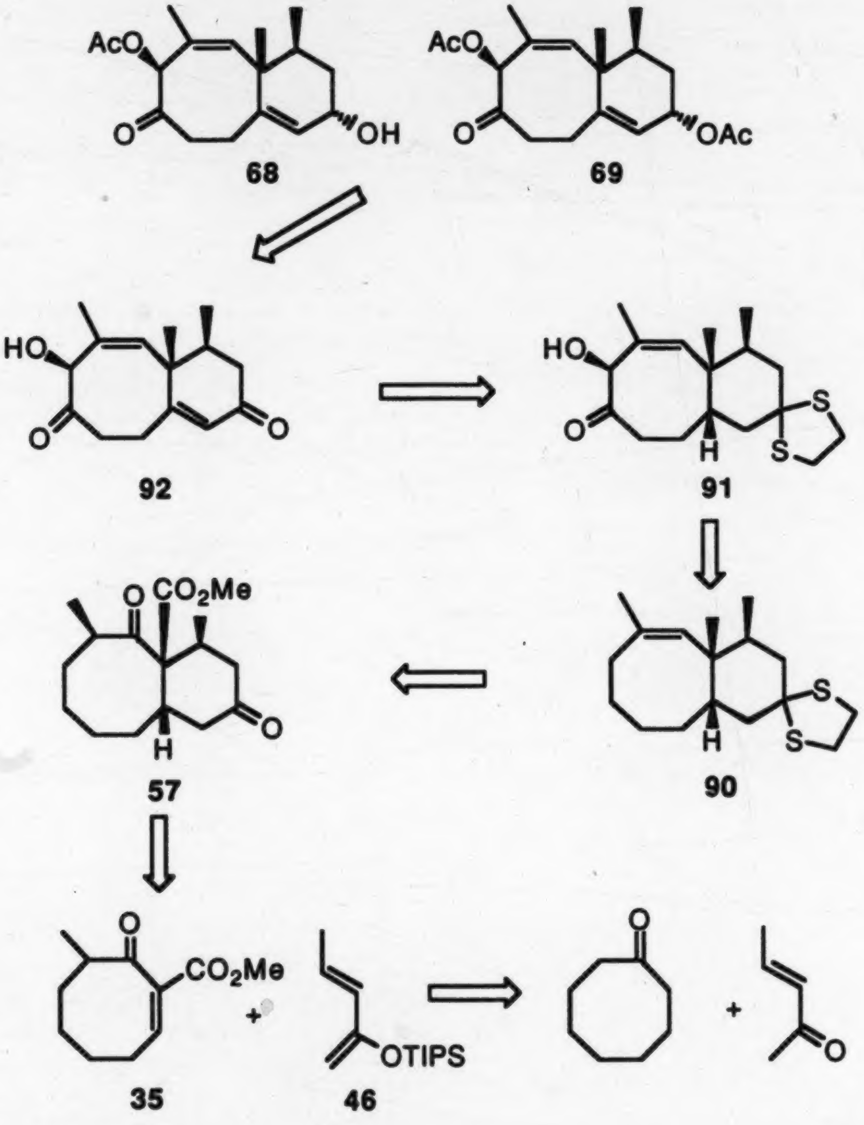


In the preparation of compound **69**, treatment of compound **88**, the acetylation product of compound **82**, with titanium(IV) chloride gave the chloride **89**. Acetylation of **89** followed by treatment with silver trifluoracetate in refluxing benzene furnished neolemnanyl acetate (**69**) in 35% yield.

The Diels-Alder reaction has been widely used and proven to be a versatile and powerful synthetic tool in the total synthesis of many polycyclic natural products. In our previous studies, the Lewis acid catalyzed Diels-Alder reaction of 2-carboalkoxy-8-methyl-2-cyclooctenones **35** and **36** displayed synthetic promise for the rapid construction of the bicyclo[6.4.0]dodecane ring system with high stereo- and regioselectivity. In order to prove the synthetic utility of this methodology, we embarked on a project directed towards the total synthesis of neolemnane (**68**) and its acetate **69**. The retro-synthetic strategy is schematically outlined in Scheme 13.

In this strategy, the key operation is the rapid construction of the fused eight-six bicyclic ring system. As shown in Table 4 in Chapter 1, the bicyclo[6.4.0]dodecane ring skeleton found in the target molecules could be successfully constructed using the Lewis acid catalyzed Diels-Alder reaction of enones **35** and **36**. Furthermore, by a suitable choice of diene, Lewis acid catalyst, and experimental procedure, the product **57** was obtained in a high yield (98%) with the required stereocenters for the target natural products (Equation 3). The preliminary studies leading to this observation are discussed in this chapter.

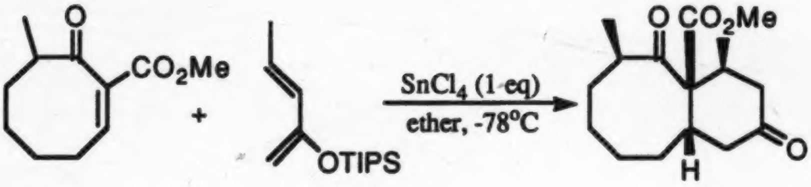
Scheme 13 The retro-synthesis of compounds **68** and **69**



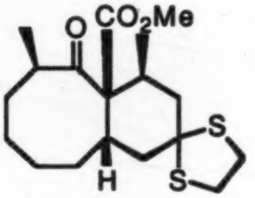
Towards the total synthesis of **68** and **69**, the cyclohexanone moiety of **57** was protected by treatment with 1,2-ethanedithiol and boron trifluoride etherate to give thioketal **93**. Then compound **93** was reduced by metal hydride reducing agents (Red-Al or DIBAL) to give diols **94** and

95. Several operations have been investigated for converting these alcohols to compound **90** *en route* to the final synthetic targets. The details of these studies are also discussed in this chapter.

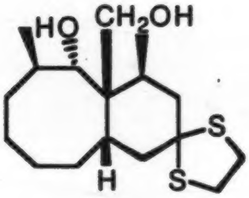
Equation 3



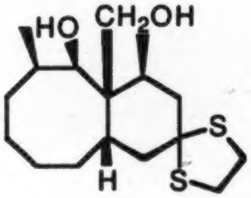
35 **46** (2 eq) **57**



93



94

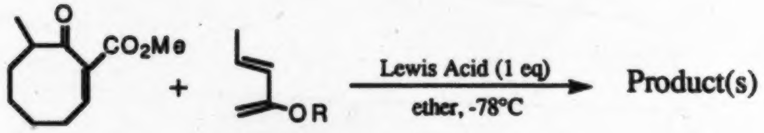


95

Results and Discussion

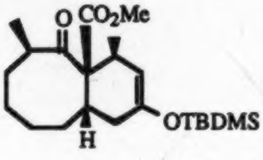
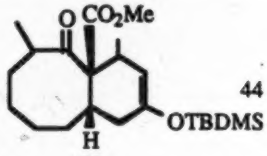
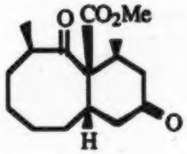
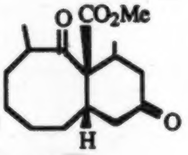
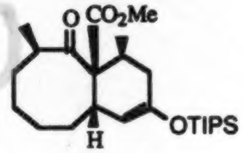
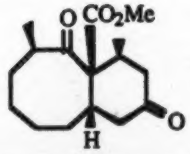
As described in the preceding section, the bicyclo[6.4.0]dodecane ring section found in neolemnane (**68**) was constructed successfully in one step by the use of the Diels-Alder reaction of enone **35** and silyloxy diene **46**. Under tin(VI) chloride catalysis, the addition occurred readily at -78°C in ether to give diketo ester **57** in excellent yield (98%). The product thus obtained was a single stereoisomer possessing stereochemistry required for the target compounds **68** and **69**. This pivotal synthetic result was obtained after a series of experimentation. Initially silyloxy diene **45** was intended for the cycloaddition reaction. Treatment of enone **35** and diene **45** at -78°C in ether using ferric chloride as a catalyst resulted in the complete consumption of the starting dienophile after 30 min (Table 5, Entry 1). Two diastereomeric adducts **54** and **55** (2 : 1), the structural assignments of which were discussed previously in Chapter 1, were obtained as an inseparable mixture in 44% yield along with a *ca*. 40% yield of an unidentified product. In the subsequent experiment, ferric chloride was replaced with a milder Lewis acid, tin(IV) chloride, as a catalyst. This resulted in a twofold increase of the yield of the Diels-Alder adducts **54** and **55** (Entry 2). However, the stereoselectivity was not improved. In another experiment, the Diels-Alder reaction was carried out involving prior complex formation between the dienophile **35** and tin(IV) chloride in ether for 20 min at -78°C (Entry 3). This was followed by the addition of diene **45**. Under these conditions no apparent improvement of the reaction was observed in terms of both yield and stereoselectivity.

Table 5. Diels-Alder reactions of 2-carbomethoxy-8-methyl-2-cyclooctenone (**35**) with dienes **45** and **46**



35

45 R = TBDMS
46 R = TIPS

Entry	Diene	Lewis Acid	Complexation time (h)	Reaction time (h)	Product(s)	Yield (%)
1[a]	**45** (10 eq)	$FeCl_3$	0	0.5	 **54** (2 : 1)  **55**	44
2[a]	**45** (10 eq)	$SnCl_4$	0	1	**54** + **55** (2 : 1)	82
3[b]	**45** (10 eq)	$SnCl_4$	0.3	1	**54** + **55** (2 : 1)	89
4[b]	**46** (10 eq)	$FeCl_3$	0.3	0.5	 **57** (4 : 1)  **96**	24
5[b]	**46** (2 eq)	$SnCl_4$	0.3	1	**57** + **96** +  (20 : 2 : 1) **56**	94
6[b]	**46** (2 eq)	$SnCl_4$	1	1	 **57** + **56** (98 : 1)	99

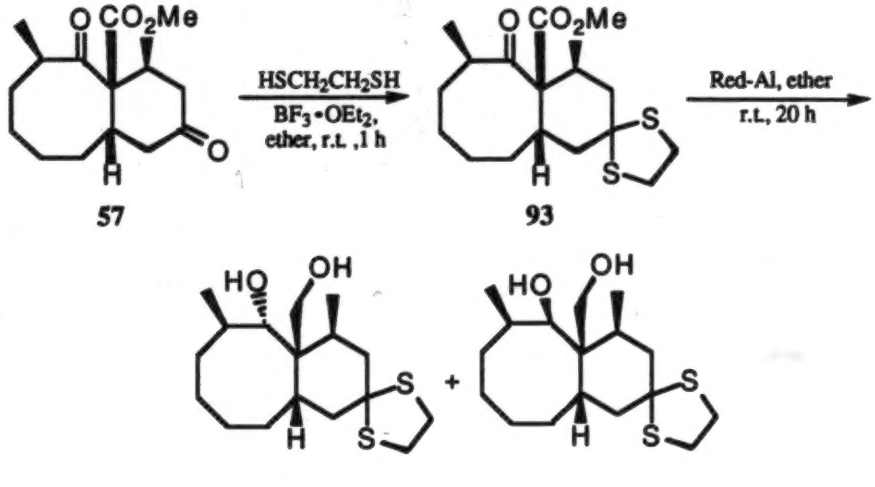
(a) Lewis acid was added to the solution of diene and dienophile. (b) Diene was added to the preformed complex of enone **35** and Lewis acid.

In principle, the Diels-Alder reaction of enone **35** with a 2-substituted *trans*-1,3-pentadiene, such as **45**, could produce four possible diastereomers. Two of these in which the allylic methyl group is *cis* to the angular carbomethoxy group (*e.g.* adduct **54**) are synthetically useful as the vicinal methyl groups in natural product **68** are *cis* to each other. Both of these desired stereoisomers are produced by addition of the diene to dienophile via an *endo*-to-ester transition state. Previous studies on the Diels-Alder reaction of a series of α-carbalkoxy α,β-unsaturated cycloalkenones[4] have demonstrated that the *endo*-to-ester transition state can be enhanced by increasing the size of the substituent attached to C-2 of *trans*-1,3-pentadiene. Under these considerations, triisopropylsilyloxy diene **46** was selected for the ensuring studies on the Diels-Alder reaction with enone **35** in order to produce a greater amount of the desired adducts resulting from *endo*-to-ester addition.

In the initial experiment, ferric chloride was again selected as the catalyst in view of its high efficiency observed for most of the Diels-Alder reactions involving **35** (see Tables 3 and 4, Chapter 1). Addition of diene **46** to an ethereal solution of preformed complex of enone **35** and ferric chloride at -78°C gave, after 30 min, an inseparable mixture of the desired compound **57** and its isomer **96** with undetermined stereochemistry in 4 : 1 ratio (Entry 4). The yield of this reaction was rather dismal (24%) as three other unidentified compounds were also produced. This poor result could be attributed to the high Lewis acidity of ferric chloride which is incompatible with the acid-sensitive silyloxy-substituted diene. Ferric chloride was thus replaced with tin(IV) chloride in the subsequent experiment. To our delight, treatment of enone **35** with tin(IV) chloride in ether at -78°C for 20 min, followed by addition of two equivalents of diene **46**, gave a 90% yield of a 10 : 1 mixture of adducts **57** and **96** along with a small amount (4%) of compound **56** (Entry 5). Interestingly, for reasons unclear, when the period of complexation was extended from 20 min to 1 h, both the stereoselectivity and yield were enhanced, and the desired diketo ester **57** was obtained as a single stereoisomer in virtually quantitative yield (Entry 6). It is noteworthy that the triisopropylsilyl enol ether moiety in the expected Diels-Alder adduct was apparently not sufficiently stable under the acidic reaction conditions and was converted directly to the observed keto carbonyl.

Towards the total synthesis of neolemnane (**68**), the next major synthetic operation was to convert the angular ester group in **57** into a methyl group and to establish the required doublet bond between C-2 and C-3. The cyclohexanone carbonyl of **57** was first protected in the form of a cyclic dithioketal by treatment with 1,2-ethanedithiol and boron trifluoride etherate in order to carry out the ensuring reduction on the β-keto ester moiety[5] (Scheme 14). Thioketal **93** thus obtained in quantitative yield showed, in the infrared spectrum, two carbonyl absorption bands at 1734 (ester) and 1690 cm^{-1} (ketone). In the high resolution mass spectrum, the molecular ion peak was found at m/z 356.14860 which was consistent with the molecular formula $C_{18}H_{28}O_3S_2$. The ^1H NMR spectrum confirmed the presence of the thioketal group, showing a multiplet at δ 3.16 - 3.36 for a total of four methylene protons. The signals at δ 37.4, 37.6, and 66.3 in the ^{13}C NMR (APT) spectrum lent further support to the formation of the thioketal group.

Scheme 14

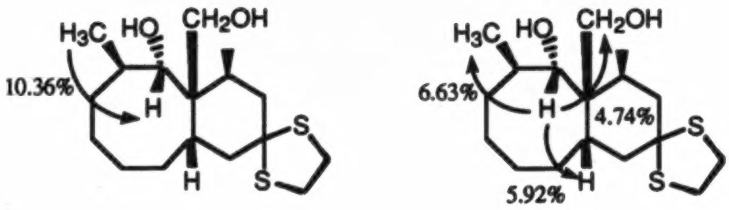


57 93 94 95

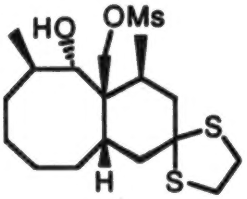
Thioketal **93** was subjected to reduction with Red-Al in ether at room temperature for 20 h. Two diastereomeric diols **94** (65% yield) and **95** (20% yield) were isolated. When the reduction was carried out with diisobutylaluminium hydride (DIBAL) in ether at room temperature for 21 h, diols **94** and **95** were obtained in 83% yield. Interestingly in this case, the latter alcohol **95** was formed as the major isomer (**94** : **95** = 1 : 1.2). Diol **94** showed an intense hydroxy absorption band at 3333 cm^{-1} in the infrared spectrum. Its molecular formula $C_{17}H_{30}O_2S_2$ was confirmed by the high resolution mass spectrum displaying a molecular ion peak at m/z 330.17095. In the ^{1}H NMR spectrum, the methine proton adjacent to the hydroxyl group appeared as a singlet at δ 4.07, while the hydroxymethylene protons were found at δ 3.80 and 3.97 as a pair of doublets with a coupling constant of 12 Hz each. In agreement with the structural assignment, the ^{13}C NMR spectrum showed two hydroxyl-bearing carbons, one at δ 67.1 (CH_2OH) and the other at δ 84.9 (CHOH).

Diol **95** displayed spectral data similar to those described above for its isomer **94**, including an intense absorption at 3440 cm^{-1} in the infrared spectrum and a molecular ion peak at m/z 330.16873 in the high resolution mass spectrum. The ^1H NMR spectrum showed a doublet δ 4.08 (J = 4.5 Hz) for the methine proton of the secondary alcohol and a pair of mutually coupled doublets at δ 3.73 and 4.04 (J = 11 Hz each) for the methlyene protons of the primary alcohol. The corresponding carbons were observed at δ 77.3 and 63.4 in the ^{13}C NMR spectrum. The stereochemistry of these two isomeric alcohols was assigned based on the NOE experiments carried out on the diol **94** (Figure 16). Results are diagrammatically compiled in Figure 16.

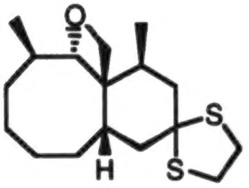
Fig. 16 The NOE results of diol **94**



Diols **94** and **95** are deemed as potentially useful synthetic intermediates. Their conversion to the projected key intermediate **90** could, in principle, be effected by selective deoxygenation of the primary alcohol followed by dehydration of the remaining hydroxyl group. One of the reliable methods for deoxygenation of a sterically hindered alcohol involves the reduction of the corresponding mesylate with zinc and sodium iodide. This method has been applied successfully on several occasions in our laboratory to compounds similar to diols **94** and **95** possessing an angular neopentyl hydroxyl. Thus, diol **94**, obtained as the major isomer from **93** via Red-Al reduction, was treated with methanesulfonyl chloride and triethylamine in dichloromethane in the presence of a small amount of *N,N*-4-dimethylaminopyridine (DMAP). After 1 h at room temperature, the corresponding mesylate **97** was obtained in quantitative yield. Its infrared spectrum showed a medium absorption at 3559 cm^{-1}, confirming the existence of the secondary hydroxyl group. The absorption bands at 1350 and 1141 cm^{-1} were attributed to the S=O vibration of the mesylate. In the ^{1}H NMR spectrum. two doublets at δ 4.57 and 4.46 (J = 10 Hz each) were assigned to the methylene protons neighboring the mesylate moiety, which in turn displayed a sharp singlet at δ 3.05. The presence of the secondary hydroxy group was verified by the singlet at δ 4.02 attributable to the adjacent methine proton. In the high resolution mass spectrum, a molecular ion peak was found at m/z 408.14549 in accordance with the molecular formula $C_{18}H_{32}O_4S_3$.

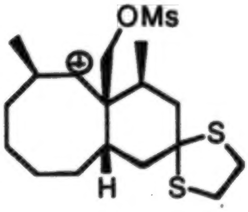


97



98

To remove its methanesulfonyloxy group, mesylate **97** was subjected to reduction with sodium iodide and zinc dust.[6] The reaction was carried out in refluxing *N,N*-dimethylformamide (DMF). A single product was obtained 85% yield. This compound, however, was shown by the following spectral data to be oxetane **98** resulting from an intramolecular displacement reaction. Both the hydroxyl and methanesulfonyl groups were absent as shown by the infrared and ^1H NMR spectra, respectively. The formation of the oxetane ring was clearly indicated by the high resolution mass spectrum which showed the molecular ion peak at m/z 312.15818 for $C_{17}H_{28}OS_2$, and by the ^1H NMR spectrum which showed a doublet (J = 2.5 Hz) at δ 4.78 and a pair of mutually coupled doublets at δ 4.44 and 4.40 (J = 6 Hz each), respectively for the methine proton and the methlyene protons on the oxetane ring. As a further confirmation, ^{13}C NMR (APT) spectrum showed signals at δ 88.2 and 73.3 for the oxygen-bearing methine and methylene carbons.



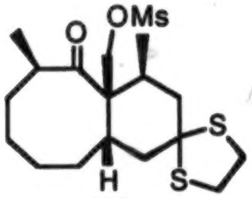
99

As shown by the preceding discussion, the secondary hydroxy group was clearly incompatible to the reaction conditions required to reduce the methanesulfonyloxy group, due to the close proximity of the two functionalities. Hence, a suitable protection of the hydroxy group was necessary prior to the reduction of the mesylate. All attempts to introduce a protecting group under basic conditions, including methylation with sodium hydride and methyl iodide[7] and silylation with trimethylsilyl chloride and sodium hydride,[8] gave inevitably oxetane **98** as the only product. On the other hand, when the protection was attempted under acidic conditions, a complex mixture was produced without exception. For instance, treatment of mesylate **97** with dihydropyran and a catalytic amount of triphenylphosphine hydrobromide[9] or with dimethoxymethane, boron trifluoride etherate and phosphorus pentoxide[10] gave, in each case, a mixture of unidentifiable products, likely arising from carbocation **99**.

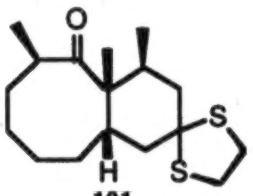
Previously in our group, a number of α-methanesulfonyloxymethyl ketones were subjected to zinc-sodium iodide reduction with variable degrees of success.[11] In view of these, hydroxy mesylate **97** was oxidized with pyridinium chlorochromate (PCC) in dichloromethane at room temperature for 30 min.[12] Keto mesylate **100** thus obtained in 60% yield showed, in the infrared spectrum, a strong carbonyl absorption at 1693 cm^{-1} at the expense of the hydroxy absorption found in that of the starting alcohol. In the high resolution mass spectrum, the molecular ion peak was found at m/z 406.13086 which was consistent with the molecular formula $C_{18}H_{30}O_4S_3$. In the ^{13}C NMR (APT) spectrum, the peak at 219.3 was due to the ketone carbonyl group.

Keto mesylate **100** was then treated with zinc dust and sodium iodide in refluxing DMF. Upon the completion of the reaction after 18 h, a single product was formed in high yield (84%). To our disappointment, however, instead of the expected ketone **101** or cyclopropanol **102**,[11] the product was found to be the undesired enol ether **103**, via cyclization. In the infrared spectrum, a medium absorption at 1730 cm^{-1} due to the enol ether C=C double bond was observed. The presence of an oxygen-bearing methylene group was evident from the pair of mutually coupled doublets at 4.53 and 4.09 (J = 5.5 Hz each) in the ^1H NMR spectrum and from the resonance at δ 52.9 in the ^{13}C NMR spectrum. The latter spectrum also confirmed the formation of the carbon-carbon double bond, showing signals at δ 154.9 and 99.7. The former signal was observed at an unusually high (δ) position apparently due to the attachment of an oxygen atom. The structural assignment was in agreement with the high resolution mass spectrum displaying a molecular ion peak at m/z 310.14210.

Some variants of the reaction conditions were also applied to the reduction of keto mesylate **100**. DMF (bp 153°C) was replaced by anhydrous diglyme (bp 162°C) of comparable bp as a solvent. After 17 h under reflux, cyclic enol ether **103** was again produced as the sole product. In another experiment, moist diglyme was used. Interestingly, this slight change of the nature of the solvent caused a drastic change of the course of the reaction. In this case, no reaction occurred probably due to hydrogen-bonding between the reactant and water.



100



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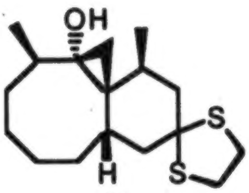
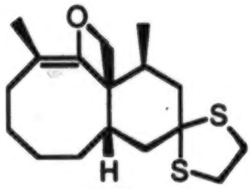


102



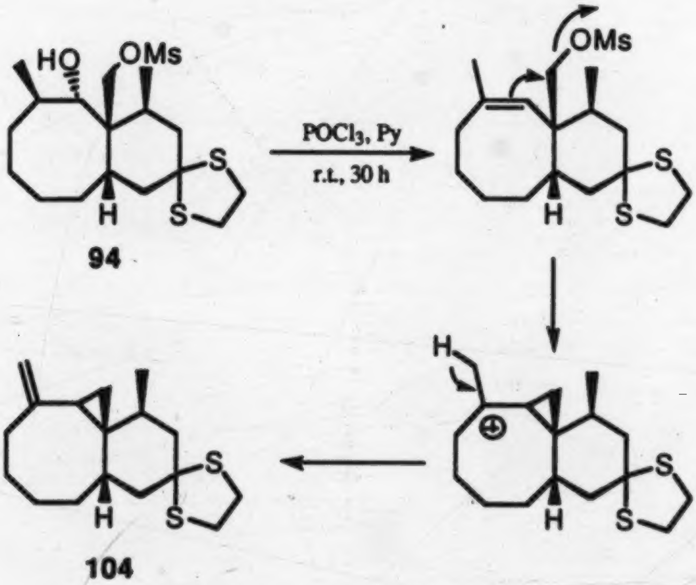
103

Compounds **98** and **103** present themselves as reasonable candidates for the preparation of the desired ketone **101** or the corresponding alcohol, as each of these compounds contains a strained four-membered ether ring which is susceptible to ring opening. Unfortunately, this could not be realized experimentally. Attempted reductive cleavage of the ether ring in **98** and **103** with DIBAL or its combination with aluminium chloride gave complex mixtures without exception.

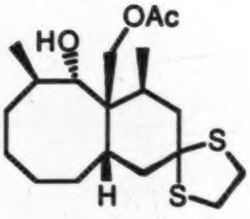
At this point, it was decided to carry out the dehydration reaction on hydroxy mesylate **97** first prior to the reductive cleavage of the methanesulfonyloxy group. After all, the resulting carbon-carbon double bond was not expected to react with the reducing agents and could survive during the required reduction process. Thus, hydroxy mesylate **97** was subjected to dehydration with phosphorus oxychloride in TEA[13] at room temperature for 30 h. Surprisingly, vinylcyclopropane **104** was formed in 90% yield, apparently as a result of dehydration followed by ring closure as shown in Scheme 17. The unusual cyclopropane ring formation was undoubtedly due to the close proximity of the double bond and the methanesulfonyloxy group. The structure of the observed product was apparent from its spectral data. The infrared spectrum indicated the presence of an exocyclic double bond, showing an absorption of medium intensity at 1642 cm^{-1}. In the ^1H NMR spectrum, the methyl signals due to the mesylate moiety and the methyl group close to the hydroxyl were absent. Instead, two singlets were observed at δ 4.75 and 4.63. These signals were readily attributed to an exocyclic methylene group. The ^1H NMR spectrum also showed three high field doublets of doublets at δ 0.62 ($J = 5.5, 8$ Hz), 0.54 ($J = 5.5, 8$ Hz), and 0.30 ($J = 5.5, 5.5$ Hz) characteristic of cyclopropyl protons. In agreement with this structural assignment the high resolution mass spectrum displayed a molecular ion peak at m/z 294.14758 for $C_{17}H_{26}S_2$.

In an alternative approach to the desired intermediate **90** from diols **94** and **95**, the dehydration of the secondary alcohol was to be carried out prior to the deoxygenation of the primary one. This approach requires the protection of the latter hydroxyl group first. For this purpose, diol **94** was subjected to silylation. Several trialkylsilyl chlorides including *tert*-butyldimethyl, triisopropyl, and trimethyl were used in conjunction with imidazole or sodium hydride as a base. Under no conditions, however, was any desired product observed. In all cases the starting diol was recovered intact.

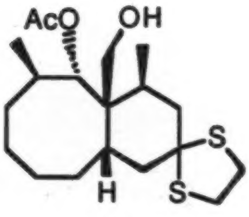
Scheme 15 The mechanistic interpretation of the formation of compound **104**



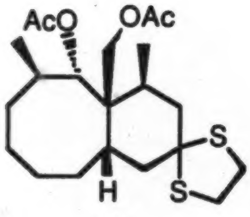
Acetylation was then attempted.[14] Treatment of diol **94** with acetic anhydride in pyridine at room temperature gave a 1 : 1 mixture of two monoacetates **105** and **106** in 92% yield along with a small amount of diacetate **107**. Diacetate **107** showed a molecular ion peak at m/z 414.18958 ($C_{21}H_{34}O_4S_2$) in the high resolution mass spectrum. The presence of an acetoxymethine unit and an acetoxymethylene unit was evident from the ^1H NMR spectrum which displayed two acetyl methyl singlets at δ 2.02 and 2.06, a doublet at δ 5.33 (J = 5 Hz) and a pair of mutually coupled doublets at δ 4.40 and 4.04 (J = 15 Hz each). The mixture of monoacetates **105** and **106** showed a molecular ion peak at m/z 372.17923 in the high resolution mass spectrum, and characteristic absorptions at 3506 (hydroxyl), 1735 and 1710 cm^{-1} (esters) in the infrared spectrum. In the ^1H NMR spectrum, two sets of signals were present in 1 : 1 ratio. Isomer **105** showed a pair of doublets at δ 4.59 and 4.20 (J = 15 Hz each) for the methylene protons adjacent to the acetoxy group and a doublet at δ 3.94 (J = 5 Hz) for the methine proton adjacent to the hydroxy group. For isomer **106**, the methine proton was observed at δ 5.38 as a doublet (J = 5 Hz) and the methylene protons appeared as a singlet at δ 3.55 due to the transposition of the acetoxy and hydroxy groups. Two singlets were observed δ 2.10 and 2.15 for the acetyl groups, respectively. The acetylation of the more hindered secondary hydroxy group at equal rate as that of the primary hydroxyl was unexpected. The observed result could be better explained by invoking an intramolecular acyl transfer process as shown in Scheme 16.



105

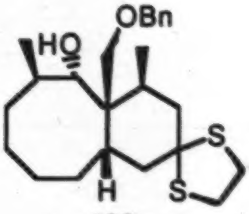


106

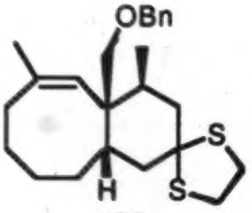


107

Selective benzylation was subsequently examined.[14] Treatment of the sodium salt derived from diol **94** and sodium hydride (1.5 eq) with benzyl bromide (1.5 eq) in ether containing a small amount of HMPA (1 eq) at room temperature for 2 h gave cleanly benzyl ether **108** in virtually quantitatively yield. The selective benzylation of the primary hydroxyl group was clearly indicated by the ^{1}H NMR spectrum which showed two pairs of doublets, one at δ 4.55 and 4.45 (J = 12 Hz each) for the benzylic protons and the other at δ 3.85 and 3.60 (J = 10 Hz) for the methylene protons neighboring the benzyloxy group. The methine proton next to the hydroxy group was found at δ 3.74 as a singlet. The assigned structure was also consistent with the high resolution mass spectrum which showed the molecular ion peak at m/z 402.20464 and with the infrared spectrum in which the hydroxy absorption appeared at 3485 cm^{-1} along with benzyl absorptions at 1530 and 1600 cm^{-1}.

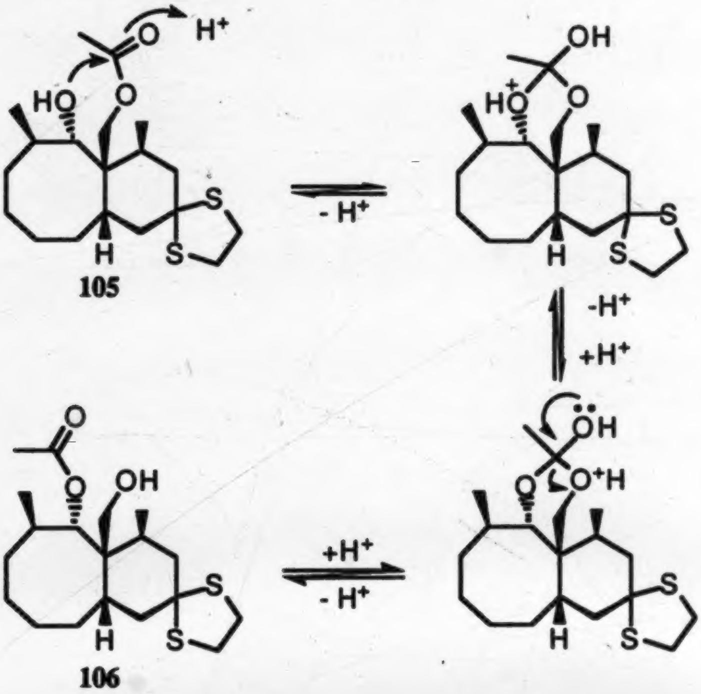


108



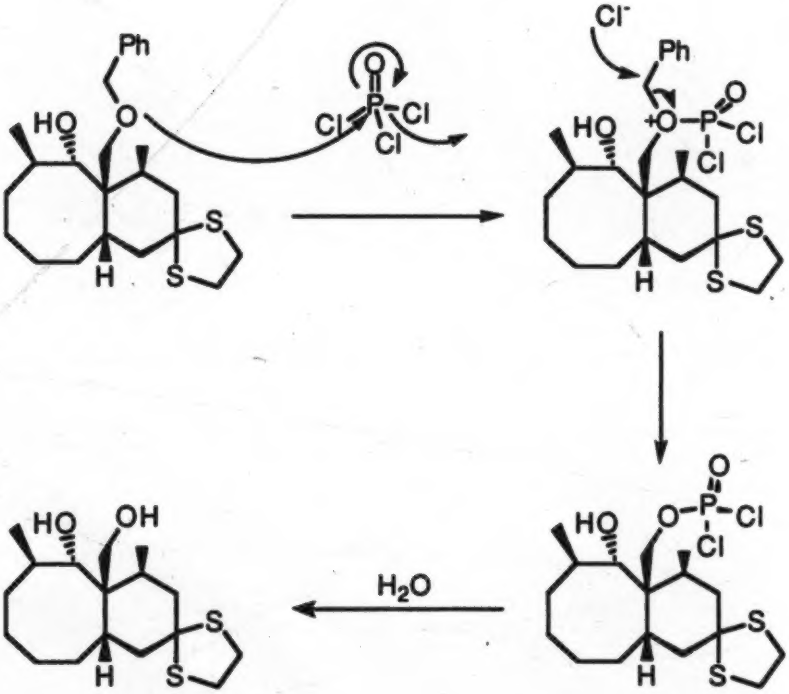
109

Scheme 16 Mechanistic interpretation of ester transposition



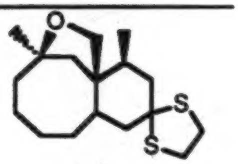
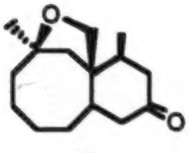
Benzyl ether **108** was found to undergo dehydration readily with phosphorus oxychloride in TEA at 60°C to give, after 8 h, the desired product **109** albeit in rather poor yield (60%). Two other products, benzyl chloride and diol **94**, were also isolated. The formation of these compounds, which could account for the low yield of **109**, suggested that a competitive debenzylation process had taken place. The debenzylation could have been induced by phosphorus oxychloride via the mechanistic pathway shown in Scheme 17. The formation of the carbon-carbon double bond was apparent from the ^{1}H NMR spectrum which showed vinylic proton at δ 5.30 as a singlet and from the absence of the hydroxyl absorption in the infrared spectrum.

Scheme 17

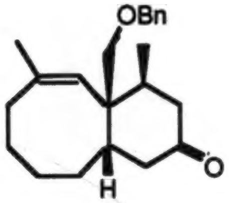


With the double bond properly installed, the required deoxygenation was then examined. Benzyl ether **109** was subjected to debenzylation with several reagents under different conditions. Results are summarized in Table 6. Treatment of benzyl ether **109** with sodium iodide and trimethylsilyl chloride[15] (Entry 1) in refluxing acetonitrile gave unexpectedly cyclic ether **110** in 80% yield. This compound was apparently produced as a result of the intramolecular cyclization of the expected alcohol upon debenzylation of **109**. The structure of **110** was established on the bases of the following spectral data. The compound was an isomer of the desired alcohol as shown by the high resolution mass spectrum which displayed a molecular ion peak at m/z 312.15778. The absence of the hydroxy group was clearly indicated by the infrared spectrum which showed no absorption band in the hydroxy range. In the ^{1}H NMR spectrum, the vinylic proton observed in the starting material was absent. Instead, a singlet was observed at δ 1.11 for the bridge head methyl group along with a methyl doublet ($J = 6.5$ Hz) at δ 1.00. The debenzylation reaction was also attempted with lithium naphthalide in THF[16] (Entry 2). A complex mixture was obtained when the reaction was carried out at room temperature, while no reaction took place at -25°C. In another attempt, benzyl ether **109** was treated with ferric chloride at 0°C in methylene chloride[17] (Entry 3). A complex mixture was again formed.

Table 6. Debenzylation results of compound **109**

entry	reagents	solvent	temp. (°C)	product
1	NaI / $(CH_3)SiCl$	CH_3CN	Reflux	 **110**
2	Lithium Naphthalenid	THF	R.T. -25°C	mess no reaction
3	$FeCl_3$	CH_2Cl_2	0°C	mess
4	1. NCS / $AgNO_3$, 2. $FeCl_3$	CH_3CN / H_2O (80%) CH_2Cl_2	R.T. 0°C	 **112**

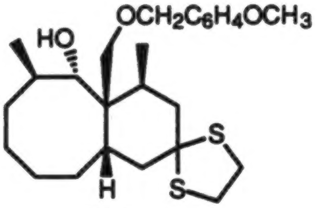
In light of the negative results under Entries 2 and 3, it was decided to convert the thioketal group in **109** to the corresponding ketone, as the formal group might have been the cause of the complication. This was effected by treatment of benzyl ether **109** with *N*-chlorosuccinamide (NCS) and silver nitrate in aqueous acetonitrile at room temperature.[18] Ketone **111** was formed cleanly in 80% yield after a short period of reaction time (5 min). In the infrared spectrum of **111**, a characteristic carbonyl band appeared at 1714 cm^{-1}. A major change of the ^1H NMR spectrum was the disappearance of the multiplet corresponding to the thioketal group in the starting material.



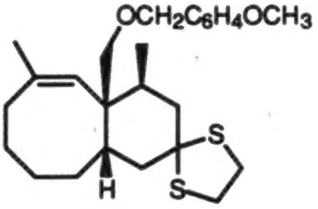
111

Ketone **111** was subjected to debenzylation with ferric chloride in methylene chloride at 0°C. In this case, the reaction occurred rather cleanly. Unfortunately, the product produced in 57% yield was the cyclic ether **112** which did not showed any hydroxy absorption in the infrared spectrum. As well, the vinylic proton was absent in ^1H NMR spectrum.

Apparently, the conditions required for debenzylation were not compatible with the existing carbon-carbon double bond, and it was necessary to replace with a different functional group which could be removed under neutral or basic conditions. With this in mind, diol **94** was converted to *p*-methoxybenzyl ether **113** (90% yield) by treatment with sodium hydride and *p*-methoxybenzyl chloride in ether at room temperature for 2.5 h.[19] The structure of **113** was verified by the infrared spectrum which showed a hydroxy absorption band at 3477 cm^{-1} and aromatic absorptions at 1513 and 1612 cm^{-1} and by the ^{1}H NMR spectrum which showed two pairs of doublets at δ 4.14, 4.03 (J = 13 Hz each), 3.75 and 3.49 (J = 11 Hz each) for the methylene protons of the angular substituent and a singlet at δ 4.38 for the methine proton of the secondary alcohol.



113

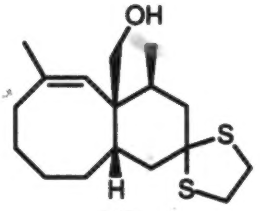


114

Dehydration of **113** with phosphorus oxychloride in TEA at 60°C, after 4 h, gave the desired product **114** in 60% yield. This compound showed the absence of hydroxy absorption in the infrared spectrum and the presence of a vinylic proton (singlet at δ 5.25) in the ^{1}H NMR spectrum. Its molecular formula of $C_{25}H_{36}O_2S_2$ was confirmed by the high resolution mass spectrum displaying a molecular ion peak at m/z 432.21367.

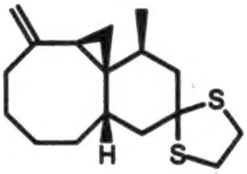
The *p*-methoxybenzyl protecting group could be easily removed oxidatively using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane.[19] The desired alcohol **115** was obtained in 66% yield after 5 h at room temperature. The infrared spectrum showed the diagnostic hydroxy band at 3455 cm^{-1}. The ^{1}H NMR spectrum indicated that the double bond was intact with the retention of a vinylic proton at δ

5.30. The structural assignment was further confirmed by the high resolution mass spectrum displaying a molecular ion peak at m/z 312.15817.

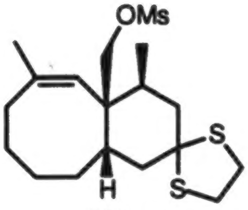


115

The stage was set for the removal of the hydroxy group. Towards this end, the formation of the corresponding mesylate, which could then be reductively cleaved by sodium iodide and zinc dust, was attempted. Interestingly, treatment of **115** with methanesulfonyl chloride in pyridine at room temperature gave, instead of the expected mesylate **116**, a high yield (86%) of vinylcyclopropane **104**, previously obtained from hydroxy mesylate **97** (*vide supra*).



104



116

Clearly, in order to transform alcohol **115** to the projected intermediate **90**, a different deoxygenation procedure has to be applied, *e.g.*, via dissolving metal reduction of the corresponding *N,N,N',N'*-tetramethylphosphorodiamidate.[20] It is also possible that vinylcyclopropane **104** could serve as an intermediate leading to olefin **90** as its vinylcyclopropyl group could be conceivably reduced by dissolving metal to the corresponding functionality found in **90**.[21] These transformations constitute our synthetic efforts currently underway towards the total synthesis of neolemnane (**68**) and its acetate **69**.

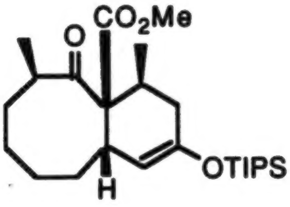
In conclusion, the Diels-Alder approach to the bicyclo[6.4.0]dodecane ring system developed in our laboratory has been successfully applied to the formation of the nucleus of a growing number of natural products possessing six-eight fused ring system. Several advanced intermediates in a projected total synthesis of neolemnane (**68**) and its acetate **69** have been effectively prepared.

Experimental

General Procedures and Materials

Refer to Chapter 1, Experimental Section for a detailed description of general procedures and materials.

(1R*, 3R*, 8R*, 12S*)-1-Carbomethoxy-10-tirisopropylsilyloxy-3,12-dimethylbicyclo[6.4.0]dodec-9-en-2-one (56) and (1R*, 3R*, 8S*, 12S*)-1-Carbomethoxy-3,12-dimethylbicyclo-[6.4.0]dodecane-2,10-dione (57)



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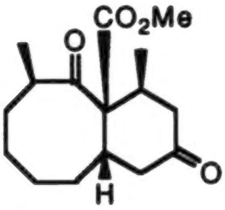
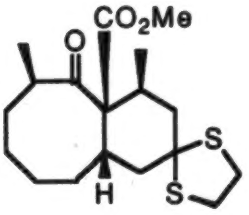


57

Refer to Chapter 1, Experimental Section for details of the experimental procedure.

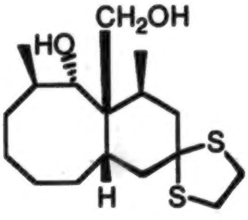
(1R*, 3R*, 8S*, 12S*)-1-Carbomethoxy-10,10-ethylenedithio-3,12-dimethylbicyclo[6.4.0]dodecan-2-one (93)



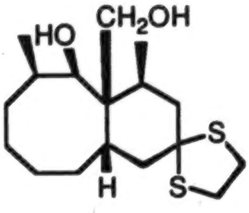
At room temperature, 1,2-ethanedithiol (25.4 mg, 0.27 mmol) was added to the ethereal solution (5 mL) of **57** (50 mg, 0.18 mmol) and boron trifluoride etherate (0.022 mL, 0.18 mmol, 1 eq) under an argon atmosphere. After stirring for one hour, the reaction was quenched by addition of water. The aqueous layer was extracted with ether 3 times (10 mL each). The organic layers were combined and washed with aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography on silica gel eluting with 8% ether in Skelly B to give thioketal **93** (57 mg, 100%) as white crystals with mp. 104 - 105°C (1% EtOAc in hexane).

IR ($CHCl_3$ cast): 1734 (C=O, ester), 1690 (C=O, ketone), 1377 cm^{-1} (CH_3); ^1H NMR (300 MHz in $CDCl_3$) δ: 3.75 (s, 3H, OCH_3), 3.36 - 3.16 (m, 4H, SCH_2CH_2S), 2.73 (m, 1H, CH, ring juntion), 2.53 (m, 1H, $CHCH_3CO$), 2.3 - 2.2 (m, 2H, CHHCHCHH, C-7 and C-9), 1.12 (d, 3H, J = 7 Hz, CH_3), 1.08 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (75 MHz in $CDCl_3$) δ: 217.4 (p), 172.6 (p), 69.8 (p), 66.3 (p), 51.8 (a), 49.4 (p), 46.0 (p), 40.6 (a), 39.9 (a), 39.8 (p), 37.7 (p), 37.4 (p), 31.4 (a), 29.9 (p), 28.4 (p), 23.3 (p), 20.1 (a), 18.5 (a); HRMS: m/z (M^+) cacld. for $C_{18}H_{28}O_3S_2$: 356.14798; found 356.14860. Anal. calcd. for $C_{18}H_{28}O_3S_2$: C 60.64%, H 7.93%, S 17.98%; found C 60.63%, H 7.94%, S 18.04%.

(1R*, 2S*, 3R*, 8S*, 12S*)-10,10-Ethylenedithio-1-hydroxymethyl-3,12-dimethylbicyclo[6.4.0]dodecan-2-ol (94) and (1R*, 2R*, 3R*, 8S*, 12S*)-10,10-Ethylenedithio-1-hydroxymethyl-3,12-dimethylbicyclo[6.4.0]dodecan-2-ol (95)



94



95

1. Reduction with Red-Al

To the ethereal solution (50 mL) of cyclic dithioketal **93** (535 mg, 1.5 mmol) was added an excess amount (1.5 mL, 65% in toluene, 7.5 mmol, 5 eq) of Red-Al at room temperature under an argon atmosphere. After stirring overnight, the reaction mixture was cooled to 0°C, and quenched by addition of aqueous saturated ammonium chloride solution until the bubbling ceased. Then 2M HCl was added dropwise until the white precipitate disappeared. The aqueous layer was extracted with ether 3 times (15 mL each). The organic layers were combined and washed with aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL), and aqueous saturated sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography eluting with 10% ethyl acetate in Skelly B to give two diastereomers **94** (321 mg, 65% yield) and **95** (99 mg 20% yield).

2. Reduction with DIBAL

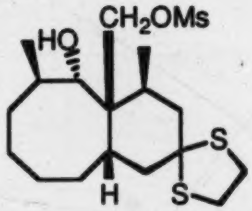
To the benzene solution of cyclic dithioketal **93** (220 mg, 0.62 mmol) was added an excess amount (3.25 mL, 3.2 mmol, 5 eq, 1.0 M in toluene) of DIBAL at room temperature under an argon atmosphere. After stirring for 21 h, the reaction mixture was cooled to 0°C, and quenched by addition of aqueous saturated ammonium chloride solution until the bubbling ceased. Then 2N HCl was added dropwise until the white precipitate disappeared. The organic layer was separated and the aqueous layer was extracted with ether three time (15 mL each). The organic layers were combined and washed with aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL), and aqueous saturated sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 10% ethyl acetate in Skelly B gave two diastereomers **94** (77.7 mg, 38% yield) and **95** (91 mg, 45% yield).

Isomer **94**: mp 160-162°C (hexane); IR (CH_2Cl_2 cast): 3333 cm^{-1} (OH); ^{1}H NMR (300 MHz in $CDCl_3$) δ: 4.07 (s, br, 1H, CHOH), 3.97 (d, 1H, J = 12 Hz, CHHOH), 3.80 (d, 1H, J = 12 Hz, CHHOH), 3.4 - 3.2 (m, 4H, SCH_2CH_2S), 2.58 (dd, 1H, J = 4, 12 Hz, $CHHCS_2C_2H_4$), 2.39 (m, 1H, CH, ring junction), 2.35 (s, br, 2H, 2OH), 2.25 - 2.15 (m, 2H, $CHCH_3$ and CHCO), 1.0 (d, 3H, J = 7 Hz, CH_3), 0.8 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (75 MHz in $CDCl_3$) δ: 84.9 (a), 67.1 (p), 66.4 (p), 50.2 (p), 45.1 (p), 44.1 (p), 39.8 (p), 37.4 (p), 34.9 (a), 33.4 (p), 30.4 (a), 30.2 (p), 30.1 (a), 28.3

(p), 26.1 (a), 25.9 (p), 16.2 (a); HRMS: m/z (M^+) calcd. for $C_{17}H_{30}O_2S_2$: 330.16873; found: 330.17095.

Isomer **95**: IR ($CHCl_3$, cast): 3440 cm^{-1} (OH); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.08 (d, 1H, J = 4.5 Hz, CHOH), 4.04 (d, 1H, J = 11 Hz, CHHOH), 3.73 (d, 1H, J = 11 Hz, CHHOH), 3.4 - 3.2 (m, 4H, SCH_2CH_2S), 1.07 (d, 3H, J = 7 Hz, CH_3), 1.04 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 77.3 (a), 66.6 (p), 63.4 (p), 60.4 (p), 49.1 (p), 46.7 (p), 45.4 (p), 40.8 (a), 39.8 (p), 37.8 (p), 35.8 (p), 32.1 (a), 31.7 (p), 30.2 (a), 26.4 (p), 18.2 (a), 18.4 (a); HRMS: m/z (M^+) calcd. for $C_{17}H_{30}O_2S_2$: 330.16873; found: 330.16570.

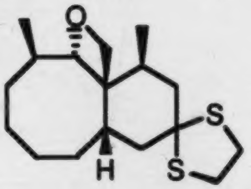
(1R*, 2S*, 3R*, 8S*, 12S*)-10,10-Ethylenedithio-1-mesyloxymethyl-3,12-dimethylbicyclo[6.4.0]dodecan-2-ol (97)



To the dichloromethane solution (5 mL) of the diol **94** (50 mg, 0.15 mmol) were added TEA (0.025 mL, 0.18 mmol, 1.2 eq), DMAP (catalytic amount) and methanesulfonyl chloride (0.014 mL, 0.18 mmol, 1.2 eq) sequentially at room temperature under an argon atmosphere. After 1 h, the reaction was quenched by addition of 2N HCl. The aqueous layer was extracted with dichloromethane 3 times (10 mL each). Then the organic layers were combined and washed with 2N HCl (10 mL), water (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL), and aqueous saturated sodium chloride solution (10 mL), dried over magnesium sulfate, filtered and concentrated to give the crude product (72 mg) as a pale yellow oil. The crude product was purified by flash chromatography on silica gel eluting with 15% ethyl acetate in Skelly B to give the monomesylate **96** (60 mg, 100% yield) as white crystals, mp 139 - 141°C (50% EtOAc in hexane).

IR ($CHCl_3$, cast): 3559 (OH), 1350 and 1141 cm^{-1} (S=O); ^1H NMR (300 MHz, $CDCl_3$), δ: 4.57 (d, 1H, J = 10 Hz, CHHOMs), 4.46 (d, 1H, J = 10 Hz, CHHOMs), 4.02 (s, br, 1H, CHOH), 3.40 - 3.20 (m, 4H, SCH_2CH_2S), 3.05 (s, 3H, SO_2CH_3), 1.04 (d, 3H, J = 7 Hz, CH_3), 0.96 (d, 3H, J = 7 Hz, $CH_3CHC=O$); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 72.8 (p), 66.0 (p), 50.0 (p), 47.5 (p), 46.3 (p), 41.7 (p), 38.0 (a), 37.5 (p), 37.3 (a), 33.4 (p), 31.3 (p), 30.5 (a), 30.2 (a), 28.0 (p), 26.5 (a), 26.2 (p), 17.1 (a), 14.2 (a); HRMS m/z (M^+) calcd. for $C_{18}H_{32}O_4S_3$: 408.14627; found: 408.14549. Anal. calcd. for $C_{18}H_{32}O_4S_3$: C 52.91%, H 7.89%, S 23.54%; found C 52.92%, H 7.87%, S 23.65%.

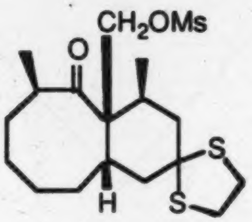
(1R*, 5R*, 10S*, 14S*)-12,12-Ethylenedithio-5,14-dimethyl-3-oxatricyclo[8.4.0.0^{1,4}]tetradecane (98)



The mixture of keto mesylate **97** (20 mg, 0.049 mmol), sodium iodide (11.8 mg, 0.49 mmol, 10 eq) and zinc dust (64.1 mg, 0.98 mmol, 20 eq) in DMF (5 mL) was refluxed under an argon atmosphere. The reaction was monitored with TLC. After 18 h, the reaction mixture was cooled to room temperature and filtered. The solid was washed with ether three times (10 mL each). The filtrate was washed with 2N HCl (10 mL) and water (10 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 5% ether in Skelly B to give the cyclic ether **98** (13.1 mg, 85% yield).

IR ($CHCl_3$, cast): 2953, 2926, 2871 cm^{-1} (C-H), 1379 cm^{-1} (CH_3); ^1H NMR (200 MHz, $CDCl_3$) δ: 4.78 (d, 1H, J = 2.5 Hz, $CHOCH_2$), 4.44 (d, 1H, J = 6 Hz, HCHOC), 4.40 (d, 1H, J = 6 Hz, HCHOC), 3.40 - 3.17 (m, 4H, SCH_2CH_2S), 2.70 (m, 1H, CH, ring junction), 1.06 (d, 3H, J = 7.5 Hz, CH_3), 1.15 (d, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 88.2 (a), 73.3 (p), 65.80 (p), 50.7 (p), 50.3 (p), 41.5 (p), 40.4 (a), 40.2 (p), 38.3 (a), 36.7 (p), 30.2 (a), 29.2 (p), 29.1 (p), 28.4 (p), 27.2 (p), 20.6 (a), 17.0 (a); HRMS: m/z (M^+) cacld. for $C_{17}H_{28}OS_2$: 312.15817; found: 312.15815.

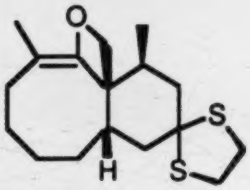
(1R*, 2S*, 3R*, 8S*, 12S*)-10,10-Ethylenedithio-1-mesyloxymethyl-3,12-dimethylbicyclo[6.4.0]dodecan-2-one (100)



To the methylene chloride solution (5 mL) of the mesylate **97** (50 mg, 0.122 mmol) was added pyridinium chlorochromate (PCC) (131.5 mg, 0.61 mmol, 5 eq) at room temperature under an argon atmosphere. After 30 min, the reaction mixture was filtered and the residue was washed with methylene chloride. The filtrate was then washed with water (10 mL), and aqueous saturated solution of sodium chloride (10 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 20% ether in Skelly B. Ketone **100** was obtained in 60% yield (30 mg) as white crystals with mp 129 - 130°C.

IR (CH_3Cl, cast): 1693 (C=O, ketone), 1354 and 1175 cm^{-1} (S=O); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.60 (d, 1H, J = 10 Hz, CHHOMs), 4.30 (d, 1H, J = 10 Hz, CHHOMs), 3.45 - 3.2 (m, 4H, SCH_2CH_2S), 3.15 (s, 3H, SO_2CH_3), 2.61 (m, 1H, CH, ring junction), 1.05 (d, 3H, J = 6 Hz, CH_3), 0.79 (d, 3H, J = 7 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 219.3 (p), 68.9 (p), 65.4 (p), 57.2 (p), 48.3 (p), 44.1 (p), 40.0 (p), 39.7 (a), 37.8 (p), 37.6 (p), 37.5 (a), 37.2 (a), 31.7 (p), 30.4 (p), 28.1 (p), 24.0 (p), 20.3 (a), 17.3 (a); HRMS: m/z (M^+) calcd. for $C_{18}H_{30}O_4S_3$: 406.13062, found: 406.13086.

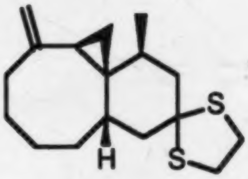
(1R*, 10S*, 14S*)-12,12-Ethylenedithio-5,14-dimethyl-3-oxa-tricyclo[8.4.0.0^{1,4}]tetradec-4-ene (103)



The mixture of keto mesylate **100** (35 mg, 0.086 mmol), sodium iodide (129 mg, 0.86 mmol, 10 eq) and zinc dust (112 mg, 1.72 mmol, 20 eq) in DMF (10 mL) was refluxed under an argon atmosphere. The reaction was monitored with TLC. After 18 h, the reaction mixture was cooled to room temperature and filtered. The solid was washed with ether three times (10 mL each). The filtrate was washed with 2N HCl (10 mL) and water (10 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 5% ether in Skelly B to give the cyclic enol ether **103** (22.4 mg, 84% yield).

IR ($CHCl_3$, cast): 1730 cm^{-1} (=C-O); ^1H NMR (300 MHz, $CDCl_3$) δ: 4.53 (d, 1H, J = 5.5 Hz, OCHH), 4.09 (d, 1H, J = 5.5 Hz, OCHH), 3.4 - 3.21 (m, 4H, SCH_2CH_2S), 1.47 (S, 3H, CH_3C=), 1.08 (d, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 154.9 (p), 99.7 (p), 74.8 (p), 66.3 (p), 52.9 (p), 49.3 (a), 49.1 (p), 44.7 (p), 40.3 (p), 37.6 (p), 29.1 (p), 28.1 (a), 26.5 (p), 26.3 (p), 16.0 (a), 12.1 (a); HRMS: m/z (M^+) cacld. for $C_{17}H_{26}OS_2$: 310.14252, found: 310.14210.

(1S*, 2R*, 8S*, 12S*)-10,10-Ethylenedithio-12-methyl-2-methylenetricyclo[10.1.0.0^{1,8}]tridecane (104)



1. From 97

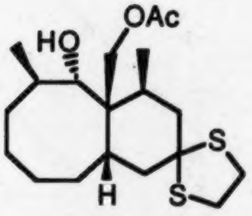
At room temperature, to the TEA solution (5 mL) of **97** (50 mg, 0.12 mmol) was added the freshly distilled phosphorus oxychloride (94 mg, 0.6 mmol, 5 eq) under an argon atmosphere. After 30 h, the reaction mixture was diluted with ether, and ice-cold water was added to destroy the excess amount of phosphorus oxychloride. Then the organic layer was separated and the aqueous layer was extracted with ether three times (10 mL each). The organic layers were combined, and dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography. Elution with 2.5% ether in Skelly B gave the pure **104** (31 mg, 90% yield) as a colorless oil.

2. From **115**

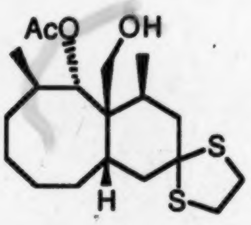
To the pyridine solution (5 mL) of **115** (63 mg, 0.2 mmol), methanesulfonyl chloride (35 mg, 0.3 mmol, 1.5 eq) was added. After 1 h, the reaction mixture was cooled to 0°C, and water was added. The organic layer was separated and the aqueous layer was extracted with ether three times (10 mL each). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography. Elution with 2.5% ether in Skelly B gave the product **104** (50.1 mg, 86% yield) as a colorless oil.

IR ($CHCl_3$, cast): 3074 (=C-H), 3058 (C-H on cyclopropane), 1642 cm^{-1} (C=C); ^1H NMR (200 MHz, $CDCl_3$) δ: 4.75 (s, 1H, =CHH), 4.63 (s, 1H, =CHH), 3.4 - 3.15 (m, 4H, SCH_2CH_2S), 0.62 (dd, 1H, J = 5.5, 8 Hz, CH on cyclopropane), 0.60 (d, 3H, J = 7 Hz, CH_3), 0.54 (dd, 1H, J = 5.5, 8 Hz, CHH on cyclopropane), 0.30 (dd, 1H, J = 5.5, 5.5 Hz, CHH on cyclopropane); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 147.8 (p), 111.7 (p), 67.6 (p), 53.1 (p), 47.2 (p), 41.2 (a), 40.5 (p), 39.0 (p), 37.3 (p), 33.4 (p), 30.3 (p), 28.6 (a), 26.5 (p), 25.0 (p), 25.96 (a), 14.9 (a), 9.5 (p); HRMS: m/z (M^+) calcd. for $C_{17}H_{26}S_2$: 294.14758; found 294.14836.

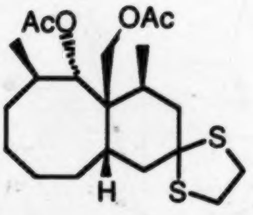
(1R*, 3R*, 8S*, 12S*)-1-Acetoxymethyl-10,10-ethylenedithio-3,12-dimethylbicyclo[6.4.0]dodecan-2-ol (105) and (1R*, 3R*, 8S*, 12S*)-10, 10-Ethylenedithio-1-hydroxymethyl-3, 12-dimethylbicyclo[6.4.0]dodec-2-yl acetate (106) and (1R*, 3R*, 8S*, 12S*)-1-Acetoxymethyl-10,10-ethylenedithio-3,12-dimethylbicyclo[6.4.0]dodec-2-yl acetate (107)



105



106



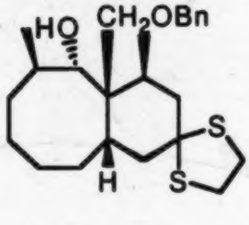
107

To the pyridine solution (10 mL) of the diol **94** (1.0 g, 3.0 mmol) were added acetic anhydride (459 mg, 4.5 mmol, 1.5 eq) and a catalytic amount of DMAP at room temperature under an argon atmosphere. After 12 h, the reaction was quenched by addition of water. The reaction mixture was neutralized by addition of aqueous saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with ether 3 times (20 mL each). The organic layers were combined, washed with water (20 mL) and aqueous saturated sodium chloride solution (20 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 10% ether in Skelly B to give a 1 : 1 mixture of **105** and **106** (1.03 g, 92% yield) and diacetate **107** (70 mg, 5.6% yield).

The mixture of **105** and **106**: IR ($CHCl_3$, cast): 3506 cm^{-1} (OH), 1735 and 1710 (C=O of two aectates); ^1H NMR (200 MHz, $CDCl_3$) δ: 4.59 (d, 0.5H, J = 15 Hz, CHHOAc, **105**), 4.20 (d, 0.5H, J = 15 Hz, CHHOAc, **105**), 3.94 (d, 0.5H, J = 4.5 Hz, CHOH, **105**), 5.38 (d, 0.5H, J = 5 Hz, CHOAc, **106**), 3.55 (s, 1H, CH_2OH, **106**), 3.40 - 3.15 (m, 4H, $2SCH_2CH_2S$ for both **105** and **106**), 2.10 (s, 1.5H, CH_3CO_2), 2.15 (s, 1.5H, CH_3CO_2), 1.06 (d, 1.5H, J = 9 Hz, CH_3) and 1.02 (d, 1.5H, J = 9 Hz, CH_3), 0.97 (d, 1.5H, J = 8.5 Hz, CH_3) and 0.93 (d, 1.5H, J = 8.5 Hz, CH_3); HRMS: m/z (M^+) calcd. for $C_{19}H_{32}O_3S_2$: 372.17929; found: 372.17923.

Diacetate **107**: ^1H NMR (200 MHz, $CDCl_3$) δ: 5.33 (d, 1H, J = 5 Hz, HCOAc), 4.40 (d, 1H, J = 15 Hz, CHHOAc), 4.04 (d, 1H, J = 15 Hz, CHHOAc), 2.02 (s, 3H, CH_3CO_2), 2.06 (s, 3H, CH_3CO_2), 1.05 (d, 3H, CH_3, J = 9 Hz), 0.97 (d, 3H, CH_3, J = 9 Hz). HRMS: m/z (M^+) calcd. for $C_{21}H_{34}O_4S_2$: 414.18985; found: 414.18958.

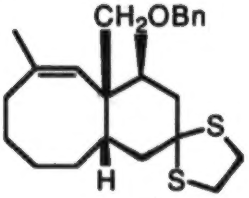
(1R*, 2S*, 8S*, 12S*)-1-Benzyloxymethyl-10,10-ethylenedithio-3,12-dimethylbicyclo[6.4.0]dodecan-2-ol (108)



At room temperature, sodium hydride (98%, 54 mg, 2.25 mmol, 5 eq) was added to the ethereal solution (15 mL) of diol **94** (150 mg, 0.456 mmol) and the resulting mixture was stirred for 30 min under an argon atmosphere. HMPA (0.11 mL, 1.5 eq) and benzyl bromide (117 mg, 0.68 mmol, 1.5 eq) were then added. After 2 h, water was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ether three times (10 mL each). The organic layers were combined, washed with 2N HCl (10 mL), water (10 mL), aqueous saturated sodium bicarbonate solution (10 mL) and aqueous saturated sodium chloride solution (10 mL), dried over magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography on silica gel. Elution with 2% ether in Skelly B gave the pure product **108** (182 mg, 95% yield) as a colorless oil.

IR ($CHCl_3$, cast): 3485 cm^{-1} (OH), 1600 and 1530 cm^{-1} (aromatic C=C); ^1H NMR (200 MHz, $CDCl_3$) δ: 7.4 - 7.15 (m, 5H, aromatic H), 4.55 (d, 1H, J = 12 Hz, OCHHPh), 4.45 (d, 1H, J = 12 Hz, OCHHPh), 3.85 (d, 1H, J = 10 Hz, OCHH), 3.60 (d, 1H, J = 10 Hz, OCHH), 3.97 (s, 1H, OH), 3.74 (d, 1H, CHOH), 3.4 - 3.2 (m, 4H, SCH_2CH_2S), 1.05 (d, 1H, J = 6 Hz, CH_3), 0.85 (d, 1H, J = 6Hz, CH_3); HRMS: m/z (M-18) cacld. for $C_{24}H_{34}OS_2$: 402.65789; found : 402.20464.

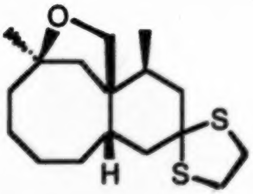
(1R*, 8S*, 12S*)-1-Benzyloxymethyl-10,10-ethylenedithio-3,12-dimethylbicyclo[6.4.0]dodec-2-ene (109)



The triethylamine solution (5 mL) of benzyl ether **108** (50 mg, 0.12 mmol) and $POCl_3$ (0.056 mL, 0.6 mmol, 5 eq) was stirred at 60ºC under an argon atmosphere. The reaction was monitored by TLC. After 4 h, the reaction mixture was cooled to 0°C and ice-cold water was added dropwise to destroy the excess amount of $POCl_3$. The organic layer was separated and the aqueous layer was extracted with ether three times (5 mL each). The organic layers were combined and washed with 2N HCl (10 mL), water (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL) and aqueous saturated sodium chloride solution (10 mL), then dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 1% ethyl acetate in Skelly B to give **109** (28.9 mg, 60% yield).

IR ($CHCl_3$, cast): 3062. and 3027 cm^{-1} (=C-H), 1096 cm^{-1} (C-O-C); ^1H NMR (200 MHz, $CDCl_3$) δ: 7.30 (m, 5H, aromatic **H**), 5.30 (s, 1H, =C**H**), 4.55 (d, 1H, J = 11 Hz, $CHHC_6H_5$), 4.46 (d, 1H, J = 11 Hz, $CHHC_6H_5$), 3.4 - 3.2 (m, 4H, SCH_2CH_2S), 1.77 (d, 3H, J = 1 Hz, $=CCH_3$), 1.0 (d, 3H, J = 6 Hz, CH_3); HRMS: m/z (M^+) calcd. for $C_{24}H_{34}OS_2$: 402.20511, found: 402.20506.

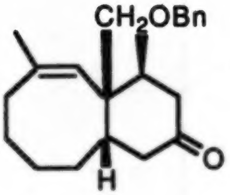
(6S*, 10S*, 11R*)-8,8-Ethylenedithio-1,10-dimethyl-13-oxa-tricyclo[9.2.1.0^{6,11}]tetradecane (110)



To the acetonitrile solution (2 mL) of benzyl ether **109** (12 mg, 0.03 mmol) and sodium iodide (4.5 mg, 0.03 mmol, 1 eq) was added trimethylsilyl chloride (3.24 mg, 0.03 mmol, 1 eq) under an argon atmosphere. The reaction was heated under reflux and monitored by TLC. After 8 h, the reaction mixture was cooled to room temperature and water was added. The aqueous layer was then extracted with ether three times (10 mL each) and the organic layers were combined and washed successively with water (10 mL) and 10% aqueous sodium thiosulfate solution twice (10 mL each) to remove inorganic salts and iodine. Then the organic solution was dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 2% ethyl acetate in Skelly B to give the product **110** (7.5 mg, 80% yield).

IR ($CHCl_3$, cast): 1073 cm^{-1} (cyclic C-O-C); ^1H NMR (200 MHz, $CDCl_3$) δ: 3.68 (d, 1H, J = 9 Hz, CHHOC), 3.45 (d, 1H, J = 9 Hz, CHHOC). 2.90 - 2.75 (m, 4H, SCH_2CH_2S), 1.11 (s, 3H, CH_3CCO), 1.00 (d, 3H, J = 6.5 Hz, CH_3); HRMS: m/z (M^+) calcd. for $C_{17}H_{28}OS_2$: 312.15817; found: 312.15778.

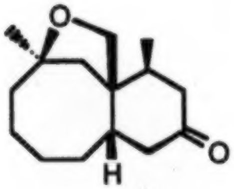
(1R*, 8S*, 12S*)-1-Benzyloxymethyl-3,12-dimethylbicyclo [6.4.0]dodec-2-en-10-one (111)



The solution of **109** (60 mg, 0.143 mmol) in acetonitrile (1 mL) was added quickly to a well stirred solution (2 mL) of NCS (77 mg, 0.572 mmol, 4 eq) and silver nitrate (109.7 mg, 0.64 mmol, 4.5 eq) in aqueous acetonitrile (1 mL, 80%) at room temperature. Silver chloride separated immediately as a voluminous white precipitate and the liquid phase became yellow in color. The reaction mixture was stirred for 3 min and treated successively at 1-min intervals with saturated aqueous sodium sulfite solution (1 mL), saturated aqueous sodium carbonate solution (1 mL) and saturates aqueous sodium chloride solution (1 mL), then 1 : 1 hexane-dichloromethane (10 mL) was added. The mixture was filtered and the residue was washed with 1 : 1 hexane-dichloromethane. The organic phase of the filtrate was separated, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 10% ethyl acetate in Skelly B to give the product **111** (37.2 mg, 80% yield).

IR ($CHCl_3$ cast): 3029 (=C-H), 1714 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$) δ: 7.25 (m, 5H, aromatic H), 5.30 (s, 1H, =CH), 4.55 (d, 1H, J = 12 Hz, OCHHPh), 4.45 (d, 1H, J = 12 Hz, OCHHPh), 1.70 (d, 3H, J = 1Hz, $=CCH_3$), 0.98 (d, 3H, J = 7.5 Hz, CH_3); HRMS: m/z (M^+) cacld. for $C_{22}H_{30}O_2$: 326.22458; found: 326.22449.

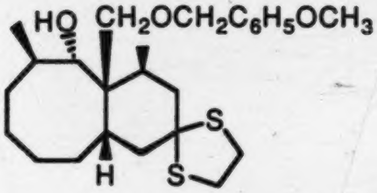
(1R*, 2S*, 6S*)-2,11-Dimethyl-12-oxatricyclo[9.2.1.0^{1,6}]-tetradecan-4-one (112)



To a stirred solution of the ketone **111** (10 mg, 0.031 mmol) in dry dichloromethane (2 mL) at 0°C under an argon atmosphere, anhydrous ferric chloride (15 mg, 0.092 mmol) was added. Stirring was continued until the color of the reaction mixture changed to brown (1 h). The reaction was quenched by addition of water (1 mL) and diluted with dichloromethane. The resulting mixture was stirred for 1 min and then extracted with dichloromethane three time (5 mL each). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 20% ethyl acetate in Skelly B to give **112** (4.2 mg, 57% yield).

IR ($CHCl_3$, cast): 1716 (C=O), 1097 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (d, 1H, J = 10 Hz, OCHHC), 3.75 (d, 1H, J = 10 Hz, OCHHC), 1.28 (s, 3H, CH_3C-O), 0.85 (d, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ: 212.2 (p), 82.2 (p), 49.1 (p) 47.0 (p), 46.6 (p), 44.0 (p), 43.8 (p),41.5 (p), 38.3 (a), 33.2 (p), 31.2 (a), 29 8 (p), 27.8 (p), 19.7 (p), 16.6 (a); HRMS: m/z (M^+) calcd. for $C_{15}H_{24}O_2$: 236.17763; found: 236.17735.

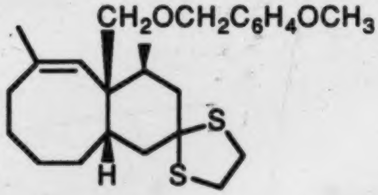
(1R*, 2S*, 3R*, 8S*, 12S*)-10,10-Ethylenedithio-1-(4-methoxybenzyloxymethyl)-3,12-dimethylbicyclo[6.4.0]dodecan-2-ol (113)



At room temperature, sodium hydride (98%, 36 mg, 1.5 mmol, 5 eq) was added to the ethereal solution of diol **94** (100 mg, 0.3 mmol). The resulting mixture was stirred for 30 min under an argon atmosphere. HMPA (0.08 mL, 1.5 eq) and *p*-methoxybenzyl chloride (70.5 mg, 0.45 mmol, 1.5 eq) were sequentially added. After 2 h, water was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ether three times (10 mL each). The organic layers were combined, washed with 2N HCl (10 mL), water (10 mL), aqueous saturated sodium bicarbonate solution (10 mL) and aqueous saturated sodium chloride solution (10 mL), then dried over magnesium sulfate, filtered and concentrated. The residue was subjected to the flash chromatography on silica gel which was pretreated with 1% TEA in Skelly B. Elution with 2.5% ether in Skelly B gave the pure product **113** (102 mg, 90% yield) as a colorless oil.

IR ($CHCl_3$, cast): 3477 (OH), 1513 and 1612 (aromatic), 1248 cm^{-1} (C-O-C); ^{1}H NMR (400 MHz, C_6D_6) δ: 7.10 (d, 2H, J = 10.5 Hz, aromatic H), 6.79 (d, 2H, J = 10.5 Hz, aromatic H), 4.14 (d, 1H, J = 13 Hz, CHHAr), 4.03 (d, 1H, J = 13 Hz, CHHAr), 4.38 (s, 1H, CHOH), 3.74 (d, 1H, J = 11 Hz, CHHO), 3.50 (d, 1H, J = 11 Hz, CHHO), 3.33 (s, 3H, OCH_3), 2.92 - 2.83 (m, 4H, SCH_2CH_2S), 1.178 (d, 3H, J = 7.5 Hz, CH_3), 0.813 (d, 3H, J = 8 Hz, CH_3); HRMS: m/z (M^+) cacld. for $C_{25}H_{38}O_3S_2$: 450.22623; found: 450.22438.

(1R*, 8S*, 12S*)-10,10-Ethylenedithio-1-(4-methoxybenzyloxymethyl)-3,12-dimethylbicyclo[6.4.0]dodec-2-ene (114)

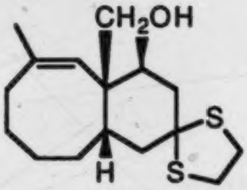


The triethylamine solution (15 mL) of benzyl ether **112** (96 mg, 0.21 mmol) and phosphorus oxychloride (0.1 mL, 1.05 mmol, 5 eq) was stirred at 60°C under an argon atmosphere. The reaction was monitored by TLC. After 8 h, the reaction mixture was cooled to 0°C and ice-cold water was added dropwise to destroy the excess amount of $POCl_3$. The organic layer was separated and the aqueous layer was washed with 2N HCl (10 mL), water (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), water (10 mL) and aqueous saturated sodium chloride solution (10 mL), then dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography eluting with 1% ethyl acetate in Skelly B to give **114** (54 mg, 60% yield) as a colorless oil.

IR ($CHCl_3$, cast): 1733 (endocyclic C=C), 1621 and 1513(C=C of phenyl), 1247 cm^{-1} (C-O-C); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.20 (d, 2H, J

= 9 Hz, aromatic H), 6.85 (d, 2H, J = 9 Hz, aromatic H), 5.25 (s, 1H, =CH), 4.45 (d, 1H, J = 12 Hz, $CHHC_6H_4$), 4.35 (d, 1H, J = 12 Hz, $CHHC_6H_4$), 3.8 (s, 3H, OCH_3), 3.4 - 3.15 (m, 6H, OCH_2, SCH_2CH_2S), 1.72 (d, 3H, J = 1 Hz, $=CCH_3$), 0.95 (d, 3H, J = 6 Hz, CH_3); HRMS: m/z (M^+) calcd. for $C_{25}H_{36}O_2S_2$: 432.21567; found: 432.21367.

(1R*, 8S*, 12S*)-10,10-Ethylenedithio-1-hydroxymethyl-3,12-dimethylbicyclo[6.4.0]dodec-2-ene (115)



To the dichloromethane-water (3 mL, 18 : 1) solution of compound **114** (84 mg, 0.19 mmol) was added DDQ (65 mg, 0.29 mmol, 1.5 eq). The reaction mixture was stirred for 5 h at room temperature. The precipitate was removed by filtration and the filtrate was concentrated and purified by flash chromatography on silica gel. Elution with 10% ethyl acetate in Skelly B gave the product **115** (35.6 mg, 60% yield) as a colorless oil.

IR ($CHCl_3$, cast): 3455 (OH), 1375 cm^{-1} (CH_3); ^1H NMR (300 MHz, $CDCl_3$) δ: 5.30 (s, 1H, =CH), 3.45 (d, 1H, J = 11.5 Hz, CHHOH), 3.30 - 3.15 (m, 5H, CHHOH, SCH_2CH_2S), 1.74 (d, 3H, J = 1 Hz, $=CCH_3$), 0.95 (d, 3H, J = 6 Hz, CH_3); HRMS: m/z (M^+) calcd. for $C_{17}H_{28}OS_2$: 312.15817; found: 312.15813.

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